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* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1           Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2           "Ask CAS" for self-help around the clock
 NEWS  3  DEC 18   CA/CAplus pre-1967 chemical substance index entries enhanced
                   with preparation role
 NEWS  4  DEC 18   CA/CAplus patent kind codes updated
 NEWS  5  DEC 18   MARPAT to CA/CAplus accession number crossover limit increased
                   to 50,000
 NEWS  6  DEC 18   MEDLINE updated in preparation for 2007 reload
 NEWS  7  DEC 27   CA/CAplus enhanced with more pre-1907 records
 NEWS  8  JAN 08   CHEMLIST enhanced with New Zealand Inventory of Chemicals
 NEWS  9  JAN 16   CA/CAplus Company Name Thesaurus enhanced and reloaded
 NEWS 10  JAN 16   IPC version 2007.01 thesaurus available on STN
 NEWS 11  JAN 16   WPIDS/WPINDEX/WPIX enhanced with IPC 8 reclassification data
 NEWS 12  JAN 22   CA/CAplus updated with revised CAS roles
 NEWS 13  JAN 22   CA/CAplus enhanced with patent applications from India
 NEWS 14  JAN 29   PHAR reloaded with new search and display fields
 NEWS 15  JAN 29   CAS Registry Number crossover limit increased to 300,000 in
                   multiple databases
 NEWS 16  FEB 15   PATDPASPC enhanced with Drug Approval numbers
 NEWS 17  FEB 15   RUSSIAPAT enhanced with pre-1994 records
 NEWS 18  FEB 23   KOREAPAT enhanced with IPC 8 features and functionality
 NEWS 19  FEB 26   MEDLINE reloaded with enhancements
 NEWS 20  FEB 26   EMBASE enhanced with Clinical Trial Number field
 NEWS 21  FEB 26   TOXCENTER enhanced with reloaded MEDLINE
 NEWS 22  FEB 26   IFICDB/IFIPAT/IFIUDB reloaded with enhancements
 NEWS 23  FEB 26   CAS Registry Number crossover limit increased from 10,000
                   to 300,000 in multiple databases
 NEWS 24  MAR 15   WPIDS/WPIX enhanced with new FRAGHITSTR display format
 NEWS 25  MAR 16   CASREACT coverage extended
 NEWS 26  MAR 20   MARPAT now updated daily
 NEWS 27  MAR 22   LWPI reloaded

 NEWS EXPRESS  NOVEMBER 10 CURRENT WINDOWS VERSION IS V8.01c, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 25 SEPTEMBER 2006.

 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS LOGIN    Welcome Banner and News Items
 NEWS IPC8     For general information regarding STN implementation of IPC 8
 NEWS X25      X.25 communication option no longer available

Enter NEWS followed by the item number or name to see news on that
specific topic.

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* * * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 19:52:59 ON 28 MAR 2007

=> file medline
COST IN U.S. DOLLARS                                  SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.21       0.21

FILE 'MEDLINE' ENTERED AT 19:53:15 ON 28 MAR 2007

 FILE LAST UPDATED: 28 Mar 2007 (20070328/UP).  FILE COVERS 1950 TO DATE.

  All regular MEDLINE updates from November 15 to December 16 have been
```

added to MEDLINE, along with 2007 Medical Subject Headings (MeSH(R)) and 2007 tree numbers.

The annual reload will be available in early 2007.

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> s (multilayer? or two layer? or bi-layer)
          5959 MULTILAYER?
       2119765 TWO
        185545 LAYER?
          2991 TWO LAYER?
                 (TWO(W)LAYER?)
        576984 BI
        146287 LAYER
            68 BI-LAYER
                 (BI(W)LAYER)
L1        8949 (MULTILAYER? OR TWO LAYER? OR BI-LAYER)

=> s (proton pump inhibitor or PPI)
         48923 PROTON
         43030 PUMP
        294262 INHIBITOR
          2210 PROTON PUMP INHIBITOR
                 (PROTON(W)PUMP(W)INHIBITOR)
          3834 PPI
L2        5534 (PROTON PUMP INHIBITOR OR PPI)

=> s antacid
L3        1898 ANTACID

=> s l1 and l2
L4           4 L1 AND L2

=> s l3 and l4
L5           0 L3 AND L4

=> s l1 and l3
L6           1 L1 AND L3

=> s l4 and l6
L7           0 L4 AND L6

=> d l4 1-4

L4   ANSWER 1 OF 4     MEDLINE on STN
Full Text
AN   2006478014     MEDLINE
DN   PubMed ID: 16466854
TI   Development of a double-layered ceramic filter for aerosol filtration at
     high-temperatures: the filter collection efficiency.
AU   de Freitas Normanda L; Goncalves Jose A S; Innocentini Murilo D M; Coury
     Jose R
CS   Chemical Engineering Department, Federal University of Sao Carlos, Via
     Washington Luiz, km 235, 13565-905 Sao Carlos, SP, Brazil.
SO   Journal of hazardous materials, (2006 Aug 25) Vol. 136, No. 3, pp. 747-56.
     Electronic Publication: 2006-02-08.
     Journal code: 9422688. ISSN: 0304-3894.
CY   Netherlands
DT   Journal; Article; (JOURNAL ARTICLE)
     (RESEARCH SUPPORT, NON-U.S. GOV'T)
LA   English
FS   Priority Journals
EM   200612
ED   Entered STN: 12 Aug 2006
     Last Updated on STN: 19 Dec 2006
     Entered Medline: 18 Dec 2006

L4   ANSWER 2 OF 4     MEDLINE on STN
Full Text
AN   2006240588     MEDLINE
```

DN PubMed ID: 16646693
TI A zero leak rate in 251 consecutive laparoscopic gastric bypass operations using a **two-layer** gastrojejunostomy technique.
AU Schweitzer Michael A; Lidor Anne; Magnuson Thomas H
CS Department of Surgery, The Johns Hopkins Medical Institute, Baltimore, Maryland 21224, USA.. mschwei7@jhmi.edu
SO Journal of laparoendoscopic & advanced surgical techniques. Part A, (2006 Apr) Vol. 16, No. 2, pp. 83-7.
Journal code: 9706293. ISSN: 1092-6429.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200610
ED Entered STN: 2 May 2006
Last Updated on STN: 21 Oct 2006
Entered Medline: 20 Oct 2006

L4 ANSWER 3 OF 4 MEDLINE on STN
Full Text
AN 2005643733 MEDLINE
DN PubMed ID: 16127662
TI Interaction of heme proteins with poly(propyleneimine) dendrimers in layer-by-layer assembly films under different pH conditions.
AU He Pingli; Li Min; Hu Naifei
CS Department of Chemistry, Beijing Normal University, Beijing 100875, China.
SO Biopolymers, (2005 Dec 15) Vol. 79, No. 6, pp. 310-23.
Journal code: 0372525. ISSN: 0006-3525.
CY United States
DT (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS Priority Journals
EM 200601
ED Entered STN: 6 Dec 2005
Last Updated on STN: 5 Jan 2006
Entered Medline: 4 Jan 2006

L4 ANSWER 4 OF 4 MEDLINE on STN
Full Text
AN 1999449139 MEDLINE
DN PubMed ID: 10520829
TI Biomarker studies in reversed Barrett's esophagus.
AU Garewal H; Ramsey L; Sharma P; Kraus K; Sampliner R; Fass R
CS Section of Hematology-Oncology, VA Medical Center and University of Arizona Health Sciences Center, Tucson 85723, USA.
SO The American journal of gastroenterology, (1999 Oct) Vol. 94, No. 10, pp. 2829-33.
Journal code: 0421030. ISSN: 0002-9270.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199910
ED Entered STN: 11 Jan 2000
Last Updated on STN: 11 Jan 2000
Entered Medline: 27 Oct 1999

=> d l6 1

L6 ANSWER 1 OF 1 MEDLINE on STN
Full Text
AN 77120867 MEDLINE
DN PubMed ID: 14246
TI Effect of chloroquine adsorption on acid reactivity of magnesium trisilicate.
AU Khalil S A
SO Journal of pharmaceutical sciences, (1977 Feb) Vol. 66, No. 2, pp. 289-90.
Journal code: 2985195R. ISSN: 0022-3549.
CY United States

```
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Priority Journals
EM   197704
ED   Entered STN: 13 Mar 1990
     Last Updated on STN: 3 Feb 1997
     Entered Medline: 15 Apr 1977


=> file ca
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                2.41       2.62

FILE 'CA' ENTERED AT 19:55:29 ON 28 MAR 2007
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FILE COVERS 1907 - 22 Mar 2007 VOL 146 ISS 14
FILE LAST UPDATED: 22 Mar 2007  (20070322/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.


=> d his

     (FILE 'HOME' ENTERED AT 19:52:59 ON 28 MAR 2007)

     FILE 'MEDLINE' ENTERED AT 19:53:15 ON 28 MAR 2007
L1          8949 S (MULTILAYER? OR TWO LAYER? OR BI-LAYER)
L2          5534 S (PROTON PUMP INHIBITOR OR PPI)
L3          1898 S ANTACID
L4             4 S L1 AND L2
L5             0 S L3 AND L4
L6             1 S L1 AND L3
L7             0 S L4 AND L6

     FILE 'CA' ENTERED AT 19:55:29 ON 28 MAR 2007

=> s (multilayer? or two layer? or bi-layer)/ab,bi
         85074 MULTILAYER?/AB
        128885 MULTILAYER?/BI
       1941233 TWO/AB
       1465949 LAYER?/AB
         10518 TWO LAYER?/AB
                 ((TWO(W)LAYER?)/AB)
       2137403 TWO/BI
       1564324 LAYER?/BI
         13960 TWO LAYER?/BI
                 ((TWO(W)LAYER?)/BI)
        114027 BI/AB
       1148673 LAYER/AB
          1020 BI-LAYER/AB
                 ((BI(W)LAYER)/AB)
        128369 BI/BI
       1245819 LAYER/BI
          1115 BI-LAYER/BI
```

```
                ((BI(W)LAYER)/BI)
L8      142581 (MULTILAYER? OR TWO LAYER? OR BI-LAYER)/AB,BI

=> s (proton pump inhibitor or PPI)/ab,bi
        154641 PROTON/AB
        103819 PUMP/AB
        346587 INHIBITOR/AB
          1233 PROTON PUMP INHIBITOR/AB
                 ((PROTON(W)PUMP(W)INHIBITOR)/AB)
        303215 PROTON/BI
        116559 PUMP/BI
        523542 INHIBITOR/BI
          2003 PROTON PUMP INHIBITOR/BI
                 ((PROTON(W)PUMP(W)INHIBITOR)/BI)
          3701 PPI/AB
          3840 PPI/BI
L9        5442 (PROTON PUMP INHIBITOR OR PPI)/AB,BI

=> s antacid/ab,bi
          1683 ANTACID/AB
          3061 ANTACID/BI
L10       3061 ANTACID/AB,BI

=> s l8 and l9
L11         14 L8 AND L9

=> s l10 and l11
L12          3 L10 AND L11

=> d 1-3

L12  ANSWER 1 OF 3  CA  COPYRIGHT 2007 ACS on STN
Full Text
AN   141:212795  CA
TI   Pharmaceutical formulation containing a proton pump inhibitor and an
     antacid
IN   Niecestro, Robert; Kositprapa, Unchalee; Oh, Yoon; Nangia, Avinash;
     Cardinal, John R.; Hahn, Elliot F.
PA   USA
SO   U.S. Pat. Appl. Publ., 12 pp.
     CODEN: USXXCO
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.         DATE
     ---------------     ----   --------    --------------------    --------
PI   US 2004166162        A1    20040826    US 2004-761805          20040121
PRAI US 2003-442337P      P     20030124

L12  ANSWER 2 OF 3  CA  COPYRIGHT 2007 ACS on STN
Full Text
AN   141:179643  CA
TI   Novel pharmaceutical formulation containing a proton pump inhibitor
     and an antacid
IN   Nicestro, Robert; Kositprapa, Unchalee; Oh, Yoon; Nangia, Avinash;
     Cardinal, John; Hahn, Elliot F.
PA   Andrx Labs LLC, USA
SO   PCT Int. Appl., 32 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.         DATE
     ---------------     ----   --------    --------------------    --------
PI   WO 2004066924        A2    20040812    WO 2004-US1434          20040121
     WO 2004066924        A3    20041007
         W:  AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG,
             BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR,
             CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES,
             ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN,
             IS, JP, JP
         RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,
```

BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK,
TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD,
TG, BF, BJ, CF, CG, CI, CM, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRAI WO 2004-US1434 20040121

L12 ANSWER 3 OF 3 CA COPYRIGHT 2007 ACS on STN
Full Text
AN 127:152954 CA
TI Oral pharmaceutical dosage forms comprising a **proton pump inhibitor** and an **antacid** agent or alginate
IN Depui, Helene; Hallgren, Agneta
PA Astra Aktiebolag, Swed.; Depui, Helene; Hallgren, Agneta
SO PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9725066	A1	19970717	WO 1996-SE1737	19961220
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2213996	A1	19970717	CA 1996-2213996	19961220
CA 2213996	C	20060829		
AU 9713241	A	19970801	AU 1997-13241	19961220
AU 712669	B2	19991111		
EP 813424	A1	19971229	EP 1996-944726	19961220
EP 813424	B1	20021120		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
BR 9607350	A	19971230	BR 1996-7350	19961220
CN 1183047	A	19980527	CN 1996-193594	19961220
CN 1080125	B	20020306		
JP 11501950	T	19990216	JP 1996-525131	19961220
HU 9904024	A2	20000528	HU 1999-4024	19961220
HU 9904024	A3	20020328		
RU 2179453	C2	20020220	RU 1997-116726	19961220
AT 228009	T	20021215	AT 1996-944726	19961220
PT 813424	T	20030331	PT 1996-944726	19961220
EE 4002	B1	20030415	EE 1997-192	19961220
ES 2185817	T3	20030501	ES 1996-944726	19961220
IL 121651	A	20030529	IL 1996-121651	19961220
SK 283695	B6	20031202	SK 1997-1169	19961220
PL 187075	B1	20040531	PL 1996-322175	19961220
CZ 293583	B6	20040616	CZ 1997-2747	19961220
TW 464514	B	20011121	TW 1996-85116139	19961227
ZA 9610935	A	19970708	ZA 1996-10935	19961230
US 6183776	B1	20010206	US 1997-750934	19970213
NO 9704071	A	19971017	NO 1997-4071	19970904
HK 1001763	A1	20030228	HK 1998-100847	19980205
HK 1017992	A1	20021101	HK 1998-111792	19981106
PRAI SE 1996-71	A	19960108		
WO 1996-SE1737	W	19961220		

=> file uspatall

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	43.59	46.21

FILE 'USPATFULL' ENTERED AT 20:03:55 ON 28 MAR 2007
CA INDEXING COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPAT2' ENTERED AT 20:03:55 ON 28 MAR 2007
CA INDEXING COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY (ACS)

```
=> s (multilayer? or two layer? or bi-layer)
L13     249524 (MULTILAYER? OR TWO LAYER? OR BI-LAYER)

=> s (multilayer? or two layer? or bi-layer)/clm
L14      41456 (MULTILAYER? OR TWO LAYER? OR BI-LAYER)/CLM

=> s (proton pump inhibitor or PPI)
L15       6631 (PROTON PUMP INHIBITOR OR PPI)

=> s (proton pump inhibitor or PPI)/clm
L16        725 (PROTON PUMP INHIBITOR OR PPI)/CLM

=> s antacid
L17       2122 ANTACID

=> s antacid/clm
L18        363 ANTACID/CLM

=> s l13 and l15
L19        741 L13 AND L15

=> s l17 and l19
L20         31 L17 AND L19

=> s l14 and l16
L21         12 L14 AND L16

=> s l18 and l21
L22          1 L18 AND L21

=> d

L22  ANSWER 1 OF 1  USPATFULL on STN
Full Text
AN      2003:250574  USPATFULL
TI      Symptomatic relief of gastrointestinal disorders
IN      Luzzatti, Renzo, Weston, FL, UNITED STATES
PI      US 2003175360       A1  20030918
AI      US 2002-79569       A1  20020222 (10)
DT      Utility
FS      APPLICATION
LN.CNT 2408
INCL    INCLM: 424/653.000
        INCLS: 424/682.000; 424/691.000; 514/304.000; 514/503.000; 514/537.000
NCL     NCLM:  424/653.000
        NCLS:  424/682.000; 424/691.000; 514/304.000; 514/503.000; 514/537.000
IC      [7]
        ICM    A61K031-46
        ICS    A61K031-29; A61K033-08; A61K033-06; A61K033-24
        IPCI   A61K0031-46 [ICM,7]; A61K0031-29 [ICS,7]; A61K0031-28 [ICS,7,C*];
               A61K0033-08 [ICS,7]; A61K0033-06 [ICS,7]; A61K0033-24 [ICS,7]
        IPCR   A61K0031-00 [I,C*]; A61K0031-00 [I,A]; A61K0033-06 [I,C*];
               A61K0033-06 [I,A]; A61K0033-24 [I,C*]; A61K0033-24 [I,A];
               A61K0045-00 [I,C*]; A61K0045-06 [I,A]; A61P0001-00 [I,C*];
               A61P0001-04 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.


=> d kwic 1

L22  ANSWER 1 OF 1  USPATFULL on STN
CLM     What is claimed is:
        1. A formulation for treating a gastrointestinal disorder comprising:
        a1) a locally acting anesthetic, and  b1) an antacid.

        13. The formulation of claim 1 wherein said antacid (b1) is an
        alkaline buffering agent.

        14. The formulation of claim 1 wherein said antacid is selected from
        the group consisting of:  a14) aluminum carbonate,  b14) aluminum
        hydroxide,  c14) aluminum phosphate,  d14) aluminum citrate,  e14).
```

. . . c17) a chewable tablet, d17) a quick dissolve tablet, e17) an effervescent tablet, f17) a multi-layer tablet, and g17) a **bi-layer** tablet; wherein said capsule (g16) is selected from the group consisting of: h17) a soft gelatin capsule, and i17) a. . .
23. The formulation of claim 1 wherein said **antacid** (b1) is provided in an amount from about 1 mEq to about 50 mEq by weight based on a total. . .
24. The formulation of claim 23 wherein said **antacid** (b1) is provided in an amount from about 5 mEq to about 40 mEq by weight based on a total. . .
25. The formulation of claim 24 wherein said **antacid** (b1) is provided in an amount from about 10 mEq to about 30 mEq by weight based on a total. . .
26. The formulation of claim 25 wherein said **antacid** (b1) is provided in an amount from about 15 mEq to about 25 mEq by weight based on a total. . .
. . . claim 29 wherein said therapeutically effective drug is selected from the group consisting of: a30) an H2 blocker; b30) a **proton pump inhibitor**; c30) an antispasm/muscle relaxing agent; d30) a prokinetic and gastrokinetic agent; e30) an antifoaming agent; f30) an anticholinergic agent; and. . .
. . . blocker (a30) is selected from the group consisting of: a31) famotidine; b31) cimetidine; c31) ranitidine; d31) nizatidine; and wherein said **proton pump inhibitor** (b30) is selected from the group consisting of: e31) omeprazole; f31) lanoprazole; g31) pantoprozole, h31) esomeprazole; i31) rabeprazole; and wherein. . .
. . . compressed tablet, a film coated tablet, a chewable tablet, a quick dissolve tablet, an effervescent tablet, a multi-layer tablet, a **bi-layer** tablet; wherein said capsule is selected from the group consisting of: a soft gelatin capsule, a hard gelatin capsule; wherein. . .
. . . claim 64 wherein said therapeutically effective drug is selected from the group consisting of: a65) an H2 blocker; b65) a **proton pump inhibitor**; c65) an antispasm/muscle relaxing agent; d65) a prokinetic and gastrokinetic agent; e65) an antifoaming agent; f65) an anticholinergic agent; and. . .
. . . blocker (a65) is selected from the group consisting of: a66) famotidine; b66) cimetidine; c66) ranitidine; d66) nizatidine; and wherein said **proton pump inhibitor** (b65) is selected from the group consisting of: e66) omeprazole; f66) lanoprazole; g66) pantoprozole; h66) esomeprazole; i66) rabeprazole; and wherein. . .
74. The formulation of claim 40 further comprising an **antacid**.

92. A formulation for treating a gastrointestinal disorder consisting essentially of: a92) a locally acting anesthetic, and b92) an **antacid**.

93. A formulation for treating a gastrointestinal disorder consisting of: a93) a locally acting anesthetic, and b93) an **antacid**.

=> d his

(FILE 'HOME' ENTERED AT 19:52:59 ON 28 MAR 2007)

FILE 'MEDLINE' ENTERED AT 19:53:15 ON 28 MAR 2007
L1 8949 S (MULTILAYER? OR TWO LAYER? OR BI-LAYER)
L2 5534 S (PROTON PUMP INHIBITOR OR PPI)
L3 1898 S ANTACID
L4 4 S L1 AND L2
L5 0 S L3 AND L4
L6 1 S L1 AND L3
L7 0 S L4 AND L6

FILE 'CA' ENTERED AT 19:55:29 ON 28 MAR 2007
L8 142581 S (MULTILAYER? OR TWO LAYER? OR BI-LAYER)/AB,BI
L9 5442 S (PROTON PUMP INHIBITOR OR PPI)/AB,BI
L10 3061 S ANTACID/AB,BI
L11 14 S L8 AND L9
L12 3 S L10 AND L11

FILE 'USPATFULL, USPAT2' ENTERED AT 20:03:55 ON 28 MAR 2007

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L13      249524 S (MULTILAYER? OR TWO LAYER? OR BI-LAYER)
L14       41456 S (MULTILAYER? OR TWO LAYER? OR BI-LAYER)/CLM
L15        6631 S (PROTON PUMP INHIBITOR OR PPI)
L16         725 S (PROTON PUMP INHIBITOR OR PPI)/CLM
L17        2122 S ANTACID
L18         363 S ANTACID/CLM
L19         741 S L13 AND L15
L20          31 S L17 AND L19
L21          12 S L14 AND L16
L22           1 S L18 AND L21

=> d l20 1-31

L20  ANSWER 1 OF 31  USPATFULL on STN
Full Text
AN      2007:69368  USPATFULL
TI      Acid secretion inhibitor
IN      Kajino, Masahiro, Osaka-shi, JAPAN
        Hasuoka, Atsushi, Osaka-shi, JAPAN
        Nishida, Haruyuki, Osaka-shi, JAPAN
PA      Takeda Pharmaceutical Company Limited, Ibaraki, JAPAN, 300-4293
        (non-U.S. corporation)
PI      US 2007060623        A1  20070315
AI      US 2006-512629       A1  20060829 (11)
PRAI    JP 2005-250356       20050820
        JP 2006-100626       20060331
DT      Utility
FS      APPLICATION
LN.CNT 7680
INCL    INCLM: 514/343.000
        INCLS: 514/424.000; 546/278.400
NCL     NCLM:  514/343.000
        NCLS:  514/424.000; 546/278.400
IC      IPCI   A61K0031-4439 [I,A]; A61K0031-4427 [I,C*]; C07D0409-14 [I,A];
               C07D0409-00 [I,C*]; C07D0403-02 [I,A]; C07D0403-00 [I,C*]

L20  ANSWER 2 OF 31  USPATFULL on STN
Full Text
AN      2007:42165  USPATFULL
TI      Orally-dispersible multilayer tablet
IN      Oury, Pascal, Le Chesnay, FRANCE
        Lamoureux, Gael, Le Boullay Thierry, FRANCE
        Herry, Catherine, Marcilly sur Eure, FRANCE
        Prevost, Yann, Tremblay Les Villages, FRANCE
PA      ETHYPHARM, Houdan, FRANCE, F-78550 (non-U.S. corporation)
PI      US 2007036861        A1  20070215
AI      US 2004-559350       A1  20040604 (10)
        WO 2004-FR1400           20040604
                                 20051205  PCT 371 date
RLI     Continuation-in-part of Ser. No. US 2003-610668, filed on 30 Jun 2003,
        PENDING
PRAI    FR 2003-6900         20030606
DT      Utility
FS      APPLICATION
LN.CNT 1101
INCL    INCLM: 424/472.000
NCL     NCLM:  424/472.000
IC      IPCI   A61K0009-24 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20  ANSWER 3 OF 31  USPATFULL on STN
Full Text
AN      2007:35958  USPATFULL
TI      Gastric acid secretion inhibiting composition
IN      Pettersson, Anders, Lilla Edet, SWEDEN
        Nystrom, Christer, Uppsala, SWEDEN
        Hakansson, Yvonne, Uppsala, SWEDEN
PA      OREXO AB, UPPSALA, SWEDEN (non-U.S. corporation)
PI      US 2007031497        A1  20070208
AI      US 2006-544750       A1  20061010 (11)
RLI     Continuation of Ser. No. US 2005-531598, filed on 25 Nov 2005, PENDING A
        371 of International Ser. No. WO 2003-SE1598, filed on 15 Oct 2003
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PRAI SE 2002-3065 20021016
DT Utility
FS APPLICATION
LN.CNT 1345
INCL INCLM: 424/473.000
INCLS: 514/338.000
NCL NCLM: 424/473.000
NCLS: 514/338.000
IC IPCI A61K0031-4439 [I,A]; A61K0031-4427 [I,C*]; A61K0009-24 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 4 OF 31 USPATFULL on STN
Full Text
AN 2006:195042 USPATFULL
TI Dosage form for treating gastrointestinal disorders
IN Plachetka, John R., Chapel Hill, NC, UNITED STATES
PA POZEN Inc., Chapel Hill, NC, UNITED STATES (U.S. corporation)
PI US 2006165797 A1 20060727
AI US 2006-328259 A1 20060110 (11)
PRAI US 2005-643137P 20050112 (60)
DT Utility
FS APPLICATION
LN.CNT 795
INCL INCLM: 424/472.000
INCLS: 514/338.000
NCL NCLM: 424/472.000
NCLS: 514/338.000
IC IPCI A61K0031-4439 [I,A]; A61K0031-4427 [I,C*]; A61K0009-24 [I,A]
IPCR A61K0031-4427 [I,C]; A61K0031-4439 [I,A]; A61K0009-24 [I,C];
A61K0009-24 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 5 OF 31 USPATFULL on STN
Full Text
AN 2006:159871 USPATFULL
TI Compositions and methods for treating pathologies that necessitate suppression of gastric acid secretion
IN Glozman, Sabina, Rehovot, ISRAEL
David, Ayelet, Negev, ISRAEL
Paul, Lada, Vancouver, CANADA
PI US 2006135406 A1 20060622
AI US 2006-351001 A1 20060209 (11)
RLI Continuation-in-part of Ser. No. US 2003-682937, filed on 14 Oct 2003, PENDING Continuation-in-part of Ser. No. WO 2004-IB2745, filed on 25 Aug 2004, PENDING
PRAI IL 2002-152289 20021014
US 2003-497930P 20030827 (60)
US 2004-544318P 20040217 (60)
US 2005-655471P 20050223 (60)
US 2005-682808P 20050520 (60)
DT Utility
FS APPLICATION
LN.CNT 1848
INCL INCLM: 514/002.000
INCLS: 514/338.000
NCL NCLM: 514/002.000
NCLS: 514/338.000
IC IPCI A61K0038-54 [I,A]; A61K0038-43 [I,C*]; A61K0031-4439 [I,A]; A61K0031-4427 [I,C*]
IPCR A61K0038-43 [I,C]; A61K0038-54 [I,A]; A61K0031-4427 [I,C]; A61K0031-4439 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 6 OF 31 USPATFULL on STN
Full Text
AN 2006:136952 USPATFULL
TI Gastric acid secretion inhibiting composition
IN Pettersson, Anders, Lilla Edet, SWEDEN
Nystrom, Christer, Uppsala, SWEDEN
Hakansson, Yvonne, Uppsala, SWEDEN
PI US 2006115530 A1 20060601
AI US 2003-531598 A1 20031015 (10)

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       WO 2003-SE1598          20031015
                               20051125  PCT 371 date
PRAI   SE 2002-3065        20021016
DT     Utility
FS     APPLICATION
LN.CNT 1343
INCL   INCLM: 424/470.000
       INCLS: 514/338.000
NCL    NCLM:  424/470.000
       NCLS:  514/338.000
IC     IPCI   A61K0031-4439 [I,A]; A61K0031-4427 [I,C*]; A61K0009-26 [I,A]
       IPCR   A61K0031-4427 [I,C]; A61K0031-4439 [I,A]; A61K0009-00 [I,C*];
              A61K0009-00 [I,A]; A61K0009-16 [N,C*]; A61K0009-16 [N,A];
              A61K0009-20 [I,C*]; A61K0009-20 [I,A]; A61K0009-24 [I,C*];
              A61K0009-24 [I,A]; A61K0009-26 [I,C]; A61K0009-26 [I,A];
              A61K0009-48 [I,C*]; A61K0009-48 [I,A]; A61K0009-50 [I,C*];
              A61K0009-50 [I,A]; A61K0031-341 [I,C*]; A61K0031-341 [I,A];
              A61K0031-4164 [I,C*]; A61K0031-4164 [I,A]; A61K0031-426 [I,C*];
              A61K0031-426 [I,A]; A61K0045-00 [I,C*]; A61K0045-06 [I,A];
              A61P0001-00 [I,C*]; A61P0001-04 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20  ANSWER 7 OF 31  USPATFULL on STN
Full Text
AN     2005:267674  USPATFULL
TI     Donepezil formulations
IN     Boehm, Garth, Westfield, NJ, UNITED STATES
       Dundon, Josephine, Fanwood, NJ, UNITED STATES
PI     US 2005232990       A1  20051020
AI     US 2004-22346       A1  20041223 (11)
PRAI   US 2003-533496P     20031231 (60)
DT     Utility
FS     APPLICATION
LN.CNT 3214
INCL   INCLM: 424/464.000
       INCLS: 514/319.000
NCL    NCLM:  424/464.000
       NCLS:  514/319.000
IC     [7]
       ICM    A61K031-445
       ICS    A61K009-20
       IPCI   A61K0031-445 [ICM,7]; A61K0009-20 [ICS,7]
       IPCR   A61K0009-20 [I,C*]; A61K0009-20 [I,A]; A61K0031-445 [I,C*];
              A61K0031-445 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20  ANSWER 8 OF 31  USPATFULL on STN
Full Text
AN     2005:220614  USPATFULL
TI     Galantamine formulations
IN     Boehm, Garth, Westfield, NJ, UNITED STATES
       Dundon, Josephine, Fanwood, NJ, UNITED STATES
PI     US 2005191349       A1  20050901
AI     US 2004-1712        A1  20041201 (11)
PRAI   US 2003-533571P     20031231 (60)
DT     Utility
FS     APPLICATION
LN.CNT 3654
INCL   INCLM: 424/464.000
       INCLS: 514/214.030; 514/397.000; 514/297.000
NCL    NCLM:  424/464.000
       NCLS:  514/214.030; 514/297.000; 514/397.000
IC     [7]
       ICM    A61K031-55
       ICS    A61K031-473; A61K031-4178; A61K009-20
       IPCI   A61K0031-55 [ICM,7]; A61K0031-473 [ICS,7]; A61K0031-4178 [ICS,7];
              A61K0031-4164 [ICS,7,C*]; A61K0009-20 [ICS,7]
       IPCR   A61K0009-20 [I,C*]; A61K0009-20 [I,A]; A61K0031-4164 [I,C*];
              A61K0031-4178 [I,A]; A61K0031-473 [I,C*]; A61K0031-473 [I,A];
              A61K0031-55 [I,C*]; A61K0031-55 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
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L20 ANSWER 9 OF 31 USPATFULL on STN
Full Text
AN 2005:63640 USPATFULL
TI Pharmaceutical compositions comprising substituted benzimidazoles and methods of using same
IN Phillips, Jeffrey O., Ashland, MO, UNITED STATES
PI US 2005054682 A1 20050310
AI US 2004-898135 A1 20040723 (10)
RLI Continuation-in-part of Ser. No. US 2003-722184, filed on 25 Nov 2003, PENDING Continuation of Ser. No. US 2002-54350, filed on 19 Jan 2002, GRANTED, Pat. No. US 6699885 Continuation-in-part of Ser. No. US 2001-901942, filed on 9 Jul 2001, GRANTED, Pat. No. US 6645988 Continuation-in-part of Ser. No. US 2000-481207, filed on 11 Jan 2000, GRANTED, Pat. No. US 6489346 Continuation-in-part of Ser. No. US 1998-183422, filed on 30 Oct 1998, ABANDONED Continuation-in-part of Ser. No. US 1996-680376, filed on 15 Jul 1996, GRANTED, Pat. No. US 5840737
PRAI US 1996-9608P 19960104 (60)
DT Utility
FS APPLICATION
LN.CNT 4983
INCL INCLM: 514/338.000
NCL NCLM: 514/338.000
IC [7]
ICM A61K031-4439
IPCI A61K0031-4439 [ICM,7]; A61K0031-4427 [ICM,7,C*]
IPCR A61K0009-00 [I,C*]; A61K0009-00 [I,A]; A61K0009-20 [I,C*]; A61K0009-20 [I,A]; A61K0009-24 [I,C*]; A61K0009-24 [I,A]; A61K0009-28 [I,C*]; A61K0009-28 [I,A]; A61K0009-46 [I,C*]; A61K0009-46 [I,A]; A61K0031-00 [I,C*]; A61K0031-00 [I,A]; A61K0031-4427 [I,C*]; A61K0031-4439 [I,A]; A61K0033-00 [I,C*]; A61K0033-00 [I,A]; A61K0045-00 [I,C*]; A61K0045-06 [I,A]; A61K0047-02 [I,C*]; A61K0047-02 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 10 OF 31 USPATFULL on STN
Full Text
AN 2005:5065 USPATFULL
TI Novel substituted benzimidazole dosage forms and method of using same
IN Phillips, Jeffrey O., Ashland, MO, UNITED STATES
PI US 2005004171 A1 20050106
AI US 2004-797374 A1 20040310 (10)
RLI Continuation of Ser. No. US 2003-722184, filed on 25 Nov 2003, PENDING Continuation of Ser. No. US 2002-54350, filed on 19 Jan 2002, GRANTED, Pat. No. US 6699885 Continuation-in-part of Ser. No. US 2001-901942, filed on 9 Jul 2001, GRANTED, Pat. No. US 6645988 Continuation-in-part of Ser. No. US 2000-481207, filed on 11 Jan 2000, GRANTED, Pat. No. US 6489346 Continuation-in-part of Ser. No. US 1998-183422, filed on 30 Oct 1998, ABANDONED Continuation-in-part of Ser. No. US 1996-680376, filed on 15 Jul 1996, GRANTED, Pat. No. US 5840737
PRAI US 1996-9608P 19960104 (60)
DT Utility
FS APPLICATION
LN.CNT 5507
INCL INCLM: 514/338.000
NCL NCLM: 514/338.000
IC [7]
ICM A61K031-4439
IPCI A61K0031-4439 [ICM,7]; A61K0031-4427 [ICM,7,C*]
IPCR A61K0009-00 [I,C*]; A61K0009-00 [I,A]; A61K0009-20 [I,C*]; A61K0009-20 [I,A]; A61K0009-24 [I,C*]; A61K0009-24 [I,A]; A61K0009-28 [I,C*]; A61K0009-28 [I,A]; A61K0009-46 [I,C*]; A61K0009-46 [I,A]; A61K0031-00 [I,C*]; A61K0031-00 [I,A]; A61K0031-4427 [I,C*]; A61K0031-4439 [I,A]; A61K0033-00 [I,C*]; A61K0033-00 [I,A]; A61K0045-00 [I,C*]; A61K0045-06 [I,A]; A61K0047-02 [I,C*]; A61K0047-02 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 11 OF 31 USPATFULL on STN
Full Text
AN 2004:314007 USPATFULL
TI **Multilayer** orodispersible tablet

IN Oury, Pascal, Le Chesnay, FRANCE
Lamoureux, Gael, Le Boullay Thierry, FRANCE
Herry, Catherine, Marcilly sur Eure, FRANCE
Prevost, Yann, Tremblay Les Villages, FRANCE
PI US 2004247677 A1 20041209
AI US 2003-610668 A1 20030630 (10)
PRAI FR 2003-6900 20030606
DT Utility
FS APPLICATION
LN.CNT 1095
INCL INCLM: 424/472.000
NCL NCLM: 424/472.000
IC [7]
ICM A61K009-24
IPCI A61K0009-24 [ICM,7]
IPCR A61K0009-00 [I,C*]; A61K0009-00 [I,A]; A61K0009-24 [I,C*];
A61K0009-24 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 12 OF 31 USPATFULL on STN
Full Text
AN 2004:239300 USPATFULL
TI Gastric retentive oral dosage form with restricted drug release in the lower gastrointestinal tract
IN Berner, Bret, El Granada, CA, UNITED STATES
Louie-Helm, Jenny, Union City, CA, UNITED STATES
PI US 2004185105 A1 20040923
AI US 2004-769574 A1 20040129 (10)
RLI Division of Ser. No. US 2001-24932, filed on 18 Dec 2001, PENDING
Continuation-in-part of Ser. No. US 2001-45816, filed on 25 Oct 2001, ABANDONED
DT Utility
FS APPLICATION
LN.CNT 2022
INCL INCLM: 424/486.000
NCL NCLM: 424/486.000
IC [7]
ICM A61K009-14
IPCI A61K0009-14 [ICM,7]
IPCR A61K0047-34 [I,C*]; A61K0047-34 [I,A]; A61K0009-00 [I,C*];
A61K0009-00 [I,A]; A61K0009-127 [I,C*]; A61K0009-127 [I,A];
A61K0009-14 [I,C*]; A61K0009-14 [I,A]; A61K0009-20 [I,C*];
A61K0009-20 [I,A]; A61K0009-22 [I,C*]; A61K0009-22 [I,A];
A61K0009-48 [I,C*]; A61K0009-48 [I,A]; A61K0009-51 [I,C*];
A61K0009-51 [I,A]; A61K0031-00 [I,C*]; A61K0031-00 [I,A];
A61K0031-165 [I,C*]; A61K0031-165 [I,A]; A61K0031-185 [I,C*];
A61K0031-195 [I,A]; A61K0031-28 [I,C*]; A61K0031-28 [I,A];
A61K0031-341 [I,C*]; A61K0031-341 [I,A]; A61K0031-4164 [I,C*];
A61K0031-4164 [I,A]; A61K0031-4196 [I,C*]; A61K0031-4196 [I,A];
A61K0031-426 [I,C*]; A61K0031-426 [I,A]; A61K0031-429 [I,C*];
A61K0031-43 [I,A]; A61K0031-4427 [I,C*]; A61K0031-4439 [I,A];
A61K0031-5375 [I,C*]; A61K0031-5377 [I,A]; A61K0031-58 [I,C*];
A61K0031-58 [I,A]; A61K0031-65 [I,C*]; A61K0031-65 [I,A];
A61K0031-7042 [I,C*]; A61K0031-7048 [I,A]; A61K0047-32 [I,C*];
A61K0047-32 [I,A]; A61K0047-36 [I,C*]; A61K0047-36 [I,A];
A61K0047-38 [I,C*]; A61K0047-38 [I,A]; A61P0001-00 [I,C*];
A61P0001-04 [I,A]; A61P0031-00 [I,C*]; A61P0031-04 [I,A];
A61P0031-06 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 13 OF 31 USPATFULL on STN
Full Text
AN 2004:221874 USPATFULL
TI Novel substituted benzimidazole dosage forms and method of using same
IN Phillips, Jeffrey O., Ashland, MO, UNITED STATES
PA THE CURATORS OF THE UNIVERSITY OF MISSOURI, Columbia, MO, UNITED STATES (U.S. corporation)
PI US 2004171646 A1 20040902
AI US 2003-722184 A1 20031125 (10)
RLI Continuation of Ser. No. US 2002-54350, filed on 19 Jan 2002, GRANTED, Pat. No. US 6699885 Continuation-in-part of Ser. No. US 2001-901942, filed on 9 Jul 2001, GRANTED, Pat. No. US 6645988 Continuation-in-part

of Ser. No. US 2000-481207, filed on 11 Jan 2000, GRANTED, Pat. No. US 6489346 Continuation-in-part of Ser. No. US 1998-183422, filed on 30 Oct 1998, ABANDONED Continuation-in-part of Ser. No. US 1996-680376, filed on 15 Jul 1996, GRANTED, Pat. No. US 5840737
PRAI US 1996-9608P 19960104 (60)
DT Utility
FS APPLICATION
LN.CNT 5487
INCL INCLM: 514/338.000
NCL NCLM: 514/338.000
IC [7]
ICM A61K031-4439
IPCI A61K0031-4439 [ICM,7]; A61K0031-4427 [ICM,7,C*]
IPCR A61K0009-00 [I,C*]; A61K0009-00 [I,A]; A61K0009-20 [I,C*]; A61K0009-20 [I,A]; A61K0009-24 [I,C*]; A61K0009-24 [I,A]; A61K0009-28 [I,C*]; A61K0009-28 [I,A]; A61K0009-46 [I,C*]; A61K0009-46 [I,A]; A61K0031-00 [I,C*]; A61K0031-00 [I,A]; A61K0031-4427 [I,C*]; A61K0031-4439 [I,A]; A61K0033-00 [I,C*]; A61K0033-00 [I,A]; A61K0045-00 [I,C*]; A61K0045-06 [I,A]; A61K0047-02 [I,C*]; A61K0047-02 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 14 OF 31 USPATFULL on STN
Full Text
AN 2004:215056 USPATFULL
TI Novel pharmaceutical formulation containing a **proton pump inhibitor** and an **antacid**
IN Niecestro, Robert, Pocono Pines, PA, UNITED STATES
Kositprapa, Unchalee, Davie, FL, UNITED STATES
Oh, Yoon, Pembroke Pines, FL, UNITED STATES
Nangia, Avinash, Weston, FL, UNITED STATES
Cardinal, John R., Tamarac, FL, UNITED STATES
Hahn, Elliot F., North Miami Beach, FL, UNITED STATES
PI US 2004166162 A1 20040826
AI US 2004-761805 A1 20040121 (10)
PRAI US 2003-442337P 20030124 (60)
DT Utility
FS APPLICATION
LN.CNT 1055
INCL INCLM: 424/472.000
INCLS: 514/339.000
NCL NCLM: 424/472.000
NCLS: 514/339.000
IC [7]
ICM A61K031-4439
ICS A61K009-24
IPCI A61K0031-4439 [ICM,7]; A61K0031-4427 [ICM,7,C*]; A61K0009-24 [ICS,7]
IPCR A61K0009-24 [I,C*]; A61K0009-24 [I,A]; A61K0031-4427 [I,C*]; A61K0031-4439 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 15 OF 31 USPATFULL on STN
Full Text
AN 2004:171513 USPATFULL
TI Gastric acid secretion inhibiting composition
IN Petterson, Anders, Kode, SWEDEN
PI US 2004131674 A1 20040708
AI US 2003-475254 A1 20031212 (10)
WO 2002-SE757 20020417
PRAI SE 2001-1379 20010418
DT Utility
FS APPLICATION
LN.CNT 913
INCL INCLM: 424/465.000
INCLS: 514/338.000
NCL NCLM: 424/465.000
NCLS: 514/338.000
IC [7]
ICM A61K031-4439
ICS A61K009-20
IPCI A61K0031-4439 [ICM,7]; A61K0031-4427 [ICM,7,C*]; A61K0009-20

[ICS,7]
IPCR A61K0031-341 [I,C*]; A61K0031-341 [I,A]; A61K0031-4164 [I,C*]; A61K0031-4164 [I,A]; A61K0031-426 [I,C*]; A61K0031-426 [I,A]; A61K0031-4427 [I,C*]; A61K0031-4439 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 16 OF 31 USPATFULL on STN
Full Text
AN 2004:82352 USPATFULL
TI Maximizing effectiveness of substances used to improve health and well being
IN Hermelin, Victor M., Chesterfield, MI, UNITED STATES
PI US 2004062802 A1 20040401
AI US 2003-644041 A1 20030820 (10)
RLI Continuation of Ser. No. US 1999-475992, filed on 30 Dec 1999, PENDING Continuation-in-part of Ser. No. US 1999-323158, filed on 1 Jun 1999, GRANTED, Pat. No. US 6214379 Continuation of Ser. No. US 1998-53487, filed on 2 Apr 1998, GRANTED, Pat. No. US 5945123
DT Utility
FS APPLICATION
LN.CNT 3143
INCL INCLM: 424/468.000
NCL NCLM: 424/468.000
IC [7]
ICM A61K009-22
IPCI A61K0009-22 [ICM,7]
IPCR A61K0009-22 [I,C*]; A61K0009-22 [I,A]; A61K0031-275 [I,C*]; A61K0031-277 [I,A]; A61K0031-4164 [I,C*]; A61K0031-4164 [I,A]; A61K0031-4458 [I,C*]; A61K0031-4458 [I,A]; A61K0031-517 [I,C*]; A61K0031-517 [I,A]; A61K0031-549 [I,C*]; A61K0031-549 [I,A]; A61K0031-551 [I,C*]; A61K0031-5513 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 17 OF 31 USPATFULL on STN
Full Text
AN 2004:64377 USPATFULL
TI Novel substituted benzimidazole dosage forms and method of using same
IN Phillips, Jeffrey Owen, Ashland, MO, UNITED STATES
PI US 2004048896 A1 20040311
AI US 2003-418410 A1 20030418 (10)
RLI Continuation of Ser. No. US 2001-901942, filed on 9 Jul 2001, GRANTED, Pat. No. US 6645988 Continuation-in-part of Ser. No. US 2000-481207, filed on 11 Jan 2000, GRANTED, Pat. No. US 6489346 Continuation-in-part of Ser. No. US 1998-183422, filed on 30 Oct 1998, ABANDONED Continuation-in-part of Ser. No. US 1996-680376, filed on 15 Jul 1996, GRANTED, Pat. No. US 5840737
PRAI US 1996-9608P 19960104 (60)
DT Utility
FS APPLICATION
LN.CNT 3917
INCL INCLM: 514/338.000
INCLS: 424/468.000
NCL NCLM: 514/338.000
NCLS: 424/468.000
IC [7]
ICM A61K031-4439
ICS A61K009-22
IPCI A61K0031-4439 [ICM,7]; A61K0031-4427 [ICM,7,C*]; A61K0009-22 [ICS,7]
IPCR A61K0009-00 [I,C*]; A61K0009-00 [I,A]; A61K0009-20 [I,C*]; A61K0009-20 [I,A]; A61K0009-22 [I,C*]; A61K0009-22 [I,A]; A61K0009-24 [I,C*]; A61K0009-24 [I,A]; A61K0009-28 [I,C*]; A61K0009-28 [I,A]; A61K0009-46 [I,C*]; A61K0009-46 [I,A]; A61K0031-00 [I,C*]; A61K0031-00 [I,A]; A61K0031-4427 [I,C*]; A61K0031-4439 [I,A]; A61K0033-00 [I,C*]; A61K0033-00 [I,A]; A61K0045-00 [I,C*]; A61K0045-06 [I,A]; A61K0047-02 [I,C*]; A61K0047-02 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 18 OF 31 USPATFULL on STN
Full Text
AN 2004:30709 USPATFULL

TI Oral pharmaceutical dosage forms comprising a **proton pump inhibitor** and a NSAID
IN Depui, Helene, Goteborg, SWEDEN
Lundberg, Per, Molndal, SWEDEN
PI US 2004022846 A1 20040205
AI US 2003-620000 A1 20030714 (10)
RLI Continuation of Ser. No. US 2002-90882, filed on 4 Mar 2002, GRANTED, Pat. No. US 6613354 Continuation of Ser. No. US 1999-471958, filed on 23 Dec 1999, GRANTED, Pat. No. US 6365184 Continuation of Ser. No. US 1997-793078, filed on 13 Feb 1997, ABANDONED A 371 of International Ser. No. WO 1996-SE1735, filed on 20 Dec 1996, UNKNOWN
PRAI SE 1996-70 19960108
DT Utility
FS APPLICATION
LN.CNT 1465
INCL INCLM: 424/452.000
INCLS: 424/465.000; 514/338.000
NCL NCLM: 424/452.000
NCLS: 424/465.000; 514/338.000
IC [7]
ICM A61K031-4439
ICS A61K009-48; A61K009-20
IPCI A61K0031-4439 [ICM,7]; A61K0031-4427 [ICM,7,C*]; A61K0009-48 [ICS,7]; A61K0009-20 [ICS,7]
IPCR A61K0009-20 [I,C*]; A61K0009-20 [I,A]; A61K0009-24 [I,C*]; A61K0009-24 [I,A]; A61K0009-28 [I,C*]; A61K0009-28 [I,A]; A61K0009-50 [I,C*]; A61K0009-50 [I,A]; A61K0045-00 [I,C*]; A61K0045-06 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 19 OF 31 USPATFULL on STN
Full Text
AN 2004:7871 USPATFULL
TI Transmucosal delivery of proton pump inhibitors
IN Widder, Kenneth, Rancho Santa Fe, CA, UNITED STATES
Hall, Warren, San Diego, CA, UNITED STATES
Olmstead, Kay, San Diego, CA, UNITED STATES
PI US 2004006111 A1 20040108
AI US 2003-353143 A1 20030127 (10)
PRAI US 2002-351909P 20020125 (60)
US 2002-374761P 20020422 (60)
DT Utility
FS APPLICATION
LN.CNT 1161
INCL INCLM: 514/338.000
INCLS: 424/471.000
NCL NCLM: 514/338.000
NCLS: 424/471.000
IC [7]
ICM A61K031-4439
ICS A61K009-24
IPCI A61K0031-4439 [ICM,7]; A61K0031-4427 [ICM,7,C*]; A61K0009-24 [ICS,7]
IPCR A61K0009-00 [I,C*]; A61K0009-00 [I,A]; A61K0009-24 [I,C*]; A61K0009-24 [I,A]; A61K0031-4427 [I,C*]; A61K0031-4439 [I,A]; A61K0033-06 [I,C*]; A61K0033-10 [I,A]; A61K0045-00 [I,C*]; A61K0045-06 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 20 OF 31 USPATFULL on STN
Full Text
AN 2003:271551 USPATFULL
TI Novel substituted benzimidazole dosage forms and method of using same
IN Phillips, Jeffrey O., Ashland, MO, UNITED STATES
PI US 2003191159 A1 20031009
US 6699885 B2 20040302
AI US 2002-54350 A1 20020119 (10)
RLI Continuation of Ser. No. US 2001-901942, filed on 9 Jul 2001, PENDING Continuation-in-part of Ser. No. US 2000-481207, filed on 11 Jan 2000, GRANTED, Pat. No. US 6489346 Continuation-in-part of Ser. No. US 1998-183422, filed on 30 Oct 1998, ABANDONED Continuation-in-part of Ser. No. US 1996-680376, filed on 15 Jul 1996, GRANTED, Pat. No. US

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       5840737
PRAI   US 1996-9608P       19960104 (60)
DT     Utility
FS     APPLICATION
LN.CNT 5446
INCL   INCLM: 514/338.000
NCL    NCLM:  514/338.000
       NCLS:  424/717.000; 514/395.000
IC     [7]
       ICM    A61K031-4439
       IPCI   A61K0031-4439 [ICM,7]; A61K0031-4427 [ICM,7,C*]
       IPCI-2 A61K0031-4439 [ICM,7]; A61K0031-4427 [ICM,7,C*]
       IPCR   A61K0009-00 [I,C*]; A61K0009-00 [I,A]; A61K0009-20 [I,C*];
              A61K0009-20 [I,A]; A61K0009-22 [I,C*]; A61K0009-22 [I,A];
              A61K0009-24 [I,C*]; A61K0009-24 [I,A]; A61K0009-28 [I,C*];
              A61K0009-28 [I,A]; A61K0009-46 [I,C*]; A61K0009-46 [I,A];
              A61K0031-00 [I,C*]; A61K0031-00 [I,A]; A61K0031-4427 [I,C*];
              A61K0031-4439 [I,A]; A61K0033-00 [I,C*]; A61K0033-00 [I,A];
              A61K0045-00 [I,C*]; A61K0045-06 [I,A]; A61K0047-02 [I,C*];
              A61K0047-02 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20  ANSWER 21 OF 31  USPATFULL on STN
Full Text
AN     2003:250574  USPATFULL
TI     Symptomatic relief of gastrointestinal disorders
IN     Luzzatti, Renzo, Weston, FL, UNITED STATES
PI     US 2003175360       A1  20030918
AI     US 2002-79569       A1  20020222 (10)
DT     Utility
FS     APPLICATION
LN.CNT 2408
INCL   INCLM: 424/653.000
       INCLS: 424/682.000; 424/691.000; 514/304.000; 514/503.000; 514/537.000
NCL    NCLM:  424/653.000
       NCLS:  424/682.000; 424/691.000; 514/304.000; 514/503.000; 514/537.000
IC     [7]
       ICM    A61K031-46
       ICS    A61K031-29; A61K033-08; A61K033-06; A61K033-24
       IPCI   A61K0031-46 [ICM,7]; A61K0031-29 [ICS,7]; A61K0031-28 [ICS,7,C*];
              A61K0033-08 [ICS,7]; A61K0033-06 [ICS,7]; A61K0033-24 [ICS,7]
       IPCR   A61K0031-00 [I,C*]; A61K0031-00 [I,A]; A61K0033-06 [I,C*];
              A61K0033-06 [I,A]; A61K0033-24 [I,C*]; A61K0033-24 [I,A];
              A61K0045-00 [I,C*]; A61K0045-06 [I,A]; A61P0001-00 [I,C*];
              A61P0001-04 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20  ANSWER 22 OF 31  USPATFULL on STN
Full Text
AN     2003:152386  USPATFULL
TI     Gastric retentive oral dosage form with restricted drug release in the
       lower gastrointestinal tract
IN     Berner, Bret, El Granada, CA, UNITED STATES
       Louie-Helm, Jenny, Union City, CA, UNITED STATES
PI     US 2003104052       A1  20030605
AI     US 2001-24932       A1  20011218 (10)
RLI    Continuation-in-part of Ser. No. US 2001-45816, filed on 25 Oct 2001,
       PENDING
DT     Utility
FS     APPLICATION
LN.CNT 2156
INCL   INCLM: 424/468.000
NCL    NCLM:  424/468.000
IC     [7]
       ICM    A61K009-22
       ICS    A61K009-14
       IPCI   A61K0009-22 [ICM,7]; A61K0009-14 [ICS,7]
       IPCR   A61K0009-00 [I,C*]; A61K0009-00 [I,A]; A61K0009-20 [N,C*];
              A61K0009-20 [N,A]; A61K0009-22 [I,C*]; A61K0009-22 [I,A];
              A61K0031-00 [I,C*]; A61K0031-00 [I,A]; A61K0031-65 [I,C*];
              A61K0031-65 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
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L20 ANSWER 23 OF 31 USPATFULL on STN
Full Text
AN 2002:279721 USPATFULL
TI Oral pharmaceutical dosage forms comprising a **proton pump inhibitor** and a NSAID
IN Depui, Helene, Goteborg, SWEDEN
Lundberg, Per, Molndal, SWEDEN
PA AstraZeneca AB. (non-U.S. corporation)
PI US 2002155153 A1 20021024
US 6613354 B2 20030902
AI US 2002-90882 A1 20020304 (10)
RLI Continuation of Ser. No. US 1999-471958, filed on 23 Dec 1999, GRANTED, Pat. No. US 6365184 Continuation of Ser. No. US 1997-793078, filed on 13 Feb 1997, ABANDONED A 371 of International Ser. No. WO 1996-SE1735, filed on 20 Dec 1996, UNKNOWN
PRAI SE 1996-70 19960108
DT Utility
FS APPLICATION
LN.CNT 1497
INCL INCLM: 424/452.000
INCLS: 424/465.000; 514/338.000
NCL NCLM: 424/458.000; 424/452.000
NCLS: 424/451.000; 424/452.000; 424/457.000; 424/465.000; 514/338.000
IC [7]
ICM A61K031-4439
ICS A61K009-48; A61K009-20
IPCI A61K0031-4439 [ICM,7]; A61K0031-4427 [ICM,7,C*]; A61K0009-48 [ICS,7]; A61K0009-20 [ICS,7]
IPCI-2 A61K0009-48 [ICM,7]; A61K0009-52 [ICS,7]; A61K0009-54 [ICS,7]; A61K0009-52 [ICS,7,C*]
IPCR A61K0009-20 [I,C*]; A61K0009-20 [I,A]; A61K0009-24 [I,C*]; A61K0009-24 [I,A]; A61K0009-28 [I,C*]; A61K0009-28 [I,A]; A61K0009-50 [I,C*]; A61K0009-50 [I,A]; A61K0009-52 [I,C*]; A61K0009-52 [I,A]; A61K0009-54 [I,A]; A61K0045-00 [I,C*]; A61K0045-06 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 24 OF 31 USPATFULL on STN
Full Text
AN 2002:85601 USPATFULL
TI Novel substituted benzimidazole dosage forms and method of using same
IN Phillips, Jeffrey O., Ashland, MO, UNITED STATES
PI US 2002045646 A1 20020418
US 6645988 B2 20031111
AI US 2001-901942 A1 20010709 (9)
RLI Continuation-in-part of Ser. No. US 2000-481207, filed on 11 Jan 2000, PENDING
DT Utility
FS APPLICATION
LN.CNT 3881
INCL INCLM: 514/338.000
NCL NCLM: 514/338.000
NCLS: 514/395.000; 546/273.700; 548/307.100
IC [7]
ICM A61K031-4439
IPCI A61K0031-4439 [ICM,7]; A61K0031-4427 [ICM,7,C*]
IPCI-2 A61K0031-4439 [ICM,7]; A61K0031-4427 [ICM,7,C*]
IPCR A61K0009-00 [I,C*]; A61K0009-00 [I,A]; A61K0009-20 [I,C*]; A61K0009-20 [I,A]; A61K0009-24 [I,C*]; A61K0009-24 [I,A]; A61K0009-28 [I,C*]; A61K0009-28 [I,A]; A61K0009-46 [I,C*]; A61K0009-46 [I,A]; A61K0031-00 [I,C*]; A61K0031-00 [I,A]; A61K0031-4427 [I,C*]; A61K0031-4439 [I,A]; A61K0033-00 [I,C*]; A61K0033-00 [I,A]; A61K0045-00 [I,C*]; A61K0045-06 [I,A]; A61K0047-02 [I,C*]; A61K0047-02 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 25 OF 31 USPATFULL on STN
Full Text
AN 2002:69628 USPATFULL
TI Oral pharmaceutical dosage forms comprising a **proton pump inhibitor** and a NSAID

IN Depui, Helene, Goteborg, SWEDEN
Lundberg, Per, Molndal, SWEDEN
PA AstraZeneca AB, Sodertalje, SWEDEN (non-U.S. corporation)
PI US 6365184 B1 20020402
AI US 1999-471958 19991223 (9)
RLI Continuation of Ser. No. US 793078, now abandoned
PRAI SE 1996-70 19960108
DT Utility
FS GRANTED
LN.CNT 1319
INCL INCLM: 424/469.000
INCLS: 424/469.000; 424/468.000; 424/464.000; 424/465.000; 424/472.000; 424/473.000; 424/471.000; 424/470.000; 424/490.000; 424/493.000; 424/494.000; 514/338.000
NCL NCLM: 424/469.000
NCLS: 424/464.000; 424/465.000; 424/468.000; 424/470.000; 424/471.000; 424/472.000; 424/473.000; 424/490.000; 424/493.000; 424/494.000; 514/338.000
IC [7]
ICM A61K009-36
ICS A61K009-26
IPCI A61K0009-36 [ICM,7]; A61K0009-30 [ICM,7,C*]; A61K0009-26 [ICS,7]
IPCR C07D0401-00 [I,C*]; C07D0401-12 [I,A]; A61K0009-20 [I,C*]; A61K0009-20 [I,A]; A61K0009-24 [I,C*]; A61K0009-24 [I,A]; A61K0009-26 [I,C*]; A61K0009-26 [I,A]; A61K0009-28 [I,C*]; A61K0009-28 [I,A]; A61K0009-30 [I,C*]; A61K0009-36 [I,A]; A61K0009-48 [I,C*]; A61K0009-48 [I,A]; A61K0009-50 [I,C*]; A61K0009-50 [I,A]; A61K0009-52 [I,C*]; A61K0009-54 [I,A]; A61K0031-185 [I,C*]; A61K0031-19 [I,A]; A61K0031-44 [I,C*]; A61K0031-44 [I,A]; A61K0031-4427 [I,C*]; A61K0031-4427 [I,A]; A61K0045-00 [I,C*]; A61K0045-06 [I,A]
EXF 424/464; 424/465; 424/472; 424/99; 424/473; 424/471; 424/468-469; 424/470; 424/474; 424/493; 424/494; 424/490; 514/338
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 26 OF 31 USPATFULL on STN
Full Text
AN 2001:18024 USPATFULL
TI Oral pharmaceutical dosage forms comprising a **proton pump inhibitor** and an **antacid** agent or alginate
IN Depui, Helene, Goteborg, Sweden
Hallgren, Agneta, Molndal, Sweden
PA Astra Aktiebolag, Sodertalje, Sweden (non-U.S. corporation)
PI US 6183776 B1 20010206
WO 9725066 19970717
AI US 1997-750934 19970213 (8)
WO 1996-SE1737 19961220
19970213 PCT 371 date
19970213 PCT 102(e) date
PRAI SE 1996-71 19960108
DT Utility
FS Granted
LN.CNT 1065
INCL INCLM: 424/468.000
INCLS: 424/469.000; 424/472.000; 424/474.000
NCL NCLM: 424/468.000
NCLS: 424/469.000; 424/472.000; 424/474.000
IC [7]
ICM A61K009-22
ICS A61K009-24; A61K009-26; A61K009-28
IPCI A61K0009-22 [ICM,7]; A61K0009-24 [ICS,7]; A61K0009-26 [ICS,7]; A61K0009-28 [ICS,7]
IPCR A61K0009-20 [I,A]; A61K0009-20 [I,C*]; A61K0009-24 [I,A]; A61K0009-24 [I,C*]; A61K0009-50 [I,A]; A61K0009-50 [I,C*]; A61K0045-00 [I,C*]; A61K0045-06 [I,A]
EXF 424/468; 424/473; 424/472; 424/469; 424/474
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 27 OF 31 USPATFULL on STN
Full Text
AN 2000:141911 USPATFULL
TI Oral pharmaceutical dosage form

IN Depui, Helene, Goteborg, Sweden
Rosinski, Adam, Molndal, Sweden
PA Astra Aktiebolag, Sodertalje, Sweden (non-U.S. corporation)
PI US 6136344 20001024
WO 9624375 19960815
AI US 1996-628712 19960415 (8)
WO 1996-SE125 19960202
19960415 PCT 371 date
19960415 PCT 102(e) date
RLI Continuation-in-part of Ser. No. US 1995-464775, filed on 7 Jun 1995, now abandoned
PRAI SE 1995-422 19950206
DT Utility
FS Granted
LN.CNT 1271
INCL INCLM: 424/470.000
INCLS: 424/464.000; 424/468.000; 424/469.000
NCL NCLM: 424/470.000
NCLS: 424/464.000; 424/468.000; 424/469.000
IC [7]
ICM A61K009-26
ICS A61K031-33
IPCI A61K0009-26 [ICM,7]; A61K0031-33 [ICS,7]
IPCR A61K0009-20 [I,A]; A61K0009-20 [I,C*]; A61K0009-28 [I,A]; A61K0009-28 [I,C*]; A61K0009-50 [I,A]; A61K0009-50 [I,C*]; A61K0045-00 [I,C*]; A61K0045-06 [I,A]
EXF 424/451; 424/457; 424/458; 424/459; 424/462; 424/464; 424/468; 424/475; 424/482; 424/469; 424/470; 514/300
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 28 OF 31 USPATFULL on STN
Full Text
AN 2000:137861 USPATFULL
TI Oral pharmaceutical dosage forms comprising a **proton pump inhibitor** and a prokinetic agent
IN Depui, Helene, Goteborg, Sweden
Hallgren, Agneta, Molndal, Sweden
PA AstraZeneca AB, Sodertalje, Sweden (non-U.S. corporation)
PI US 6132771 20001017
WO 9725065 19970717
AI US 1997-750936 19970213 (8)
WO 1996-SE1736 19961220
19970213 PCT 371 date
19970213 PCT 102(e) date
PRAI SE 1996-72 19960108
DT Utility
FS Granted
LN.CNT 1165
INCL INCLM: 424/468.000
INCLS: 424/469.000; 424/470.000; 424/475.000; 424/490.000; 424/482.000; 424/480.000; 424/460.000; 514/925.000
NCL NCLM: 424/468.000
NCLS: 424/460.000; 424/469.000; 424/470.000; 424/475.000; 424/480.000; 424/482.000; 424/490.000; 514/925.000
IC [7]
ICM A61K009-22
ICS A61K009-30; A61K009-26; A61K009-50
IPCI A61K0009-22 [ICM,7]; A61K0009-30 [ICS,7]; A61K0009-26 [ICS,7]; A61K0009-50 [ICS,7]
IPCR A61K0031-445 [I,A]; A61K0031-445 [I,C*]; A61K0045-00 [I,C*]; A61K0045-06 [I,A]
EXF 424/468; 424/465; 424/467; 424/475; 424/469; 424/494; 424/480; 424/489; 424/490; 424/470; 424/474; 424/460; 424/482; 514/925
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 29 OF 31 USPAT2 on STN
Full Text
AN 2003:271551 USPAT2
TI Substituted benzimidazole dosage forms and methods of using same
IN Phillips, Jeffrey O., Ashland, MO, United States
PA The Curators of the University of Missouri, Columbia, MO, United States (U.S. corporation)

PI US 6699885 B2 20040302
AI US 2002-54350 20020119 (10)
RLI Continuation-in-part of Ser. No. US 2001-901942, filed on 9 Jul 2001 Continuation-in-part of Ser. No..US 2000-481207, filed on 11 Jan 2000, now patented, Pat. No. US 6489346 Continuation-in-part of Ser. No. US 1998-183422, filed on 30 Oct 1998, now abandoned Continuation-in-part of Ser. No. US 1996-680376, filed on 15 Jul 1996, now patented, Pat. No. US 5840737
PRAI US 1996-9608P 19960104 (60)
DT Utility
FS GRANTED
LN.CNT 5303
INCL INCLM: 514/338.000
INCLS: 514/395.000; 424/717.000
NCL NCLM: 514/338.000
NCLS: 424/717.000; 514/395.000
IC [7]
ICM A61K031-4439
IPCI A61K0031-4439 [ICM,7]; A61K0031-4427 [ICM,7,C*]
IPCI-2 A61K0031-4439 [ICM,7]; A61K0031-4427 [ICM,7,C*]
IPCR A61K0009-00 [I,C*]; A61K0009-00 [I,A]; A61K0009-20 [I,C*]; A61K0009-20 [I,A]; A61K0009-22 [I,C*]; A61K0009-22 [I,A]; A61K0009-24 [I,C*]; A61K0009-24 [I,A]; A61K0009-28 [I,C*]; A61K0009-28 [I,A]; A61K0009-46 [I,C*]; A61K0009-46 [I,A]; A61K0031-00 [I,C*]; A61K0031-00 [I,A]; A61K0031-4427 [I,C*]; A61K0031-4439 [I,A]; A61K0033-00 [I,C*]; A61K0033-00 [I,A]; A61K0045-00 [I,C*]; A61K0045-06 [I,A]; A61K0047-02 [I,C*]; A61K0047-02 [I,A]
EXF 514/338; 514/395
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 30 OF 31 USPAT2 on STN
Full Text
AN 2002:279721 USPAT2
TI Oral pharmaceutical dosage forms comprising a **proton pump inhibitor** and a NSAID
IN Depui, Helene, Goteborg, SWEDEN
Lundberg, Per, Molndal, SWEDEN
PA AstraZeneca AB, Sodertalje, SWEDEN (non-U.S. corporation)
PI US 6613354 B2 20030902
AI US 2002-90882 20020304 (10)
RLI Continuation of Ser. No. US 1999-471958, filed on 23 Dec 1999, now patented, Pat. No. US 6365184 Continuation of Ser. No. US 793078, now abandoned
DT Utility
FS GRANTED
LN.CNT 1287
INCL INCLM: 424/458.000
INCLS: 424/451.000; 424/452.000; 424/457.000
NCL NCLM: 424/458.000; 424/452.000
NCLS: 424/451.000; 424/452.000; 424/457.000; 424/465.000; 514/338.000
IC [7]
ICM A61K009-48
ICS A61K009-52; A61K009-54
IPCI A61K0031-4439 [ICM,7]; A61K0031-4427 [ICM,7,C*]; A61K0009-48 [ICS,7]; A61K0009-20 [ICS,7]
IPCI-2 A61K0009-48 [ICM,7]; A61K0009-52 [ICS,7]; A61K0009-54 [ICS,7]; A61K0009-52 [ICS,7,C*]
IPCR A61K0009-20 [I,C*]; A61K0009-20 [I,A]; A61K0009-24 [I,C*]; A61K0009-24 [I,A]; A61K0009-28 [I,C*]; A61K0009-28 [I,A]; A61K0009-50 [I,C*]; A61K0009-50 [I,A]; A61K0009-52 [I,C*]; A61K0009-52 [I,A]; A61K0009-54 [I,A]; A61K0045-00 [I,C*]; A61K0045-06 [I,A]
EXF 424/468; 424/465; 424/474; 424/489; 424/490; 424/469; 424/464; 424/470; 424/471; 424/493; 424/494; 424/458; 424/457; 424/452; 424/451; 424/459; 424/461; 424/462
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 31 OF 31 USPAT2 on STN
Full Text
AN 2002:85601 USPAT2
TI Substituted benzimidazole dosage forms and method of using same

IN Phillips, Jeffrey O., Ashland, MO, United States
PA Curators of the University of Missouri, Columbia, MO, United States (U.S. corporation)
PI US 6645988 B2 20031111
AI US 2001-901942 20010709 (9)
RLI Continuation-in-part of Ser. No. US 2000-481207, filed on 11 Jan 2000, now patented, Pat. No. US 6489346 Continuation-in-part of Ser. No. US 1998-183422, filed on 30 Oct 1998, now abandoned Continuation-in-part of Ser. No. US 1996-680376, filed on 15 Jul 1996, now patented, Pat. No. US 5840737
PRAI US 1996-9608P 19960104 (60)
DT Utility
FS GRANTED
LN.CNT 4173
INCL INCLM: 514/338.000
INCLS: 546/273.700; 548/307.100; 514/395.000
NCL NCLM: 514/338.000
NCLS: 514/395.000; 546/273.700; 548/307.100
IC [7]
ICM A61K031-4439
IPCI A61K0031-4439 [ICM,7]; A61K0031-4427 [ICM,7,C*]
IPCI-2 A61K0031-4439 [ICM,7]; A61K0031-4427 [ICM,7,C*]
IPCR A61K0009-00 [I,C*]; A61K0009-00 [I,A]; A61K0009-20 [I,C*]; A61K0009-20 [I,A]; A61K0009-24 [I,C*]; A61K0009-24 [I,A]; A61K0009-28 [I,C*]; A61K0009-28 [I,A]; A61K0009-46 [I,C*]; A61K0009-46 [I,A]; A61K0031-00 [I,C*]; A61K0031-00 [I,A]; A61K0031-4427 [I,C*]; A61K0031-4439 [I,A]; A61K0033-00 [I,C*]; A61K0033-00 [I,A]; A61K0045-00 [I,C*]; A61K0045-06 [I,A]; A61K0047-02 [I,C*]; A61K0047-02 [I,A]
EXF 514/338
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d l20 an ti in pi kwic 9 11 15 20 22 25 26 27 28 30 31

L20 ANSWER 9 OF 31 USPATFULL on STN
Full Text
AN 2005:63640 USPATFULL
TI Pharmaceutical compositions comprising substituted benzimidazoles and methods of using same
IN Phillips, Jeffrey O., Ashland, MO, UNITED STATES
PI US 2005054682 A1 20050310
AB The present invention is directed to, inter alia, pharmaceutical compositions comprising at least one **proton pump inhibitor** and at least one buffering agent. Compositions of the invention are useful in treating, inter alia, gastric acid related disorders.
SUMM . . . an orally deliverable pharmaceutical composition comprising: (a) a therapeutically effective amount of at least one acid labile, substituted benzimidazole H+,K+-ATPase **proton pump inhibitor**; and (b) at least one buffering agent in a total amount greater than 10 mEq. In a related embodiment, the. . .
DRWD [0018] FIG. 5 is a graph illustrating environmental pH values after administration of a **proton pump inhibitor**/buffering agent formulation.
DETD . . . herein with particular reference to omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, pariprazole, or leminoprazole, it will be understood that any other **proton pump inhibitor**, if desired, can be substituted in whole or in part for the **proton pump inhibitor** described.
DETD . . . an orally deliverable pharmaceutical composition comprising: (a) a therapeutically effective amount of at least one acid labile, substituted benzimidazole H+,K+-ATPase **proton pump inhibitor**; and (b) at least one buffering agent in a total amount greater than 10 mEq; the composition comprises substantially no. . .
DETD . . . an orally deliverable pharmaceutical composition comprising: (a) a therapeutically effective amount of at least one acid labile, substituted benzimidazole H+,K+-ATPase **proton pump inhibitor**; and (b) a combination of at least two non-amino acid buffering agents, wherein the combination of at least two non-amino. .
DETD . . . an orally deliverable pharmaceutical composition comprising: (a) a therapeutically effective amount of at least one acid labile, substituted benzimidazole H+,K+-ATPase **proton pump**

inhibitor in a total amount of about 20 to about 40 mg; and (b) at least one non-amino acid buffering agent. . .

DETD . . . an orally deliverable pharmaceutical composition comprising: (a) a therapeutically effective amount of at least one acid labile, substituted benzimidazole H+,K+-ATPase **proton pump inhibitor**; and (b) at least one buffering agent in a total amount greater than 10 mEq, wherein the composition comprises substantially. . . agent is present, at least one of the following conditions is met: (1) the weight ratio of amino acid buffering agent:**proton pump inhibitor** is greater than 20:1; (2) the composition comprises at least two non-amino acid buffering agents; (3) the composition comprises at least one non-amino acid buffering agent wherein the weight ratio of the at least one non-amino acid buffering agent:**proton pump inhibitor** is greater than 20:1; and/or (4) the weight ratio of total buffering agent:**proton pump inhibitor** is greater than 40:1. In another related embodiment, if such a composition comprises a poly[phosphoryl/sulfon]-ated carbohydrate, the weight ratio of. . .

DETD [0028] Compositions of the invention comprise at least one pharmaceutically acceptable acid labile, substituted benzimidazole H+,K+-ATPase **proton pump inhibitor** (**PPI**). Illustrative PPIs are those compounds of Formula (I): ##STR1##

DETD [0040] In another embodiment, compositions of the invention comprise at least one **PPI** in a total amount of about 1 mg to about 1000 mg, about 7.5 mg to about 750 mg, about. . .

DETD . . . a weak or strong base. In one embodiment, the buffering agent, when formulated with or administered substantially simultaneously with a **PPI**, functions to raise the pH of gastrointestinal fluid and thereby to substantially prevent or inhibit acid degradation of the **PPI** by gastrointestinal fluid.

DETD . . . a composition of the invention in a total amount of about 0.05 mEq to about 10 mEq per mg of **PPI**, about 0.1 mEq to about 5 mEq per mg of **PPI**, or about 0.2 mEq to about 2.5 mEq per mg of **PPI**.

DETD [0048] In still another embodiment, one or more buffering agents and the **PPI** are present in a weight ratio of at least about 5:1, at least about 7:1, at least about 10:1, at. . .

DETD . . . a suspension tablet, a chewable tablet, an effervescent powder, an effervescent tablet, lozenge and/or a troche, the buffering agent and **PPI** are present in a weight ratio greater than 20:1, not less than about 21:1, not less than about 22:1, not. . .

DETD . . . in the composition, at least one of the following conditions is met: (1) the weight ratio of amino acid buffering agent:**proton pump inhibitor** is greater than 20:1; (2) the composition comprises at least two non-amino acid buffering agents; (3) the composition comprises at least one non-amino acid buffering agent wherein the weight ratio of the at least one non-amino acid buffering agent:**proton pump inhibitor** is greater than 20:1; and/or (4) the weight ratio of total buffering agent:**proton pump inhibitor** is greater than 40:1. In a related embodiment, the composition comprises substantially no or no amount of poly[phosphoryl/sulfon]-ated carbohydrate. In. . .

DETD . . . dosage unit, or a small plurality (i.e. up to about 4) of dosage units, provides a sufficient amount of the **PPI** to result in the desired response or effect.

DETD . . . to about 50 mg, about 15 mg to about 45 mg, or about 20 mg to about 40 mg of **PPI**. In still another embodiment, individual dosage units of the invention contain about 5 mg, about 10 mg, about 15 mg,. . . about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, or about 100 mg of **proton pump inhibitor**.

DETD . . . a single dosage unit of the invention comprises a therapeutically effective amount or a therapeutically and/or prophylactically effective amount of **PPI**. The term "therapeutically effective amount" or "therapeutically and/or prophylactically effective amount" as used herein refers to an amount of compound. . .

DETD . . . Illustratively, where the subject is a child or a small animal (e.g., a dog) a relatively low amount of the **PPI** in the dose ranges provided herein will likely provide blood serum concentrations consistent with therapeutic effectiveness. Where the subject is an adult human or a large animal (e.g., a horse), achievement of such blood serum concentrations of the **PPI** are likely to require dose units containing a relatively greater amount of the agent.

DETD [0067] Solid dosage forms such as tablets can also be prepared by mixing **PPI** with at least one pharmaceutically acceptable buffering agent as described herein above, and with one or more optional pharmaceutical

excipient. . .

DETD [0069] Compositions of the invention can be prepared utilizing micronized **PPI**, micronized buffering agent, and/or micronized pharmaceutical excipients. Micronization is the process by which solid particles are reduced in size. Since. . .

DETD [0070] In another embodiment, the present invention provides a pharmaceutical composition comprising at least one **PPI** and at least one buffering agent in a form convenient and stable for storage, whereby when the composition is placed. . . administration to a subject. Such tablets or other solid dosage forms advantageously provide for continuous and precise dosing of a **proton pump inhibitor** that may be of low solubility in water and may be particularly useful for medicating children, the elderly and others. . .

DETD . . . water or other liquid and are thereby readily form a suspension. By providing a pharmaceutical composition including omeprazole or other **proton pump inhibitor** with at least one buffering agent in a solid form that can be stored and later dissolved or suspended in. . .

DETD [0072] Suspension tablets can further comprise a disintegrant in addition to at least one **PPI**, at least one buffering agent, and optional pharmaceutical excipients. Non-limiting examples of suitable disintegrants include starches, sodium starch glycolate, clays. . .

DETD . . . composition of the invention is in the form of a solid dosage unit, the weight ratio of buffering agent to **PPI** is greater than 20:1, for example at least about 21:1, at least about 23:1, or at least about 26:1. Illustratively, in such an embodiment, the weight ratio of buffering agent to **PPI** will be greater than 20:1 and less than or equal to about 150:1; greater than or equal to about 21:1. . .

DETD . . . composition of the invention is in the form of a solid dosage unit, the weight ratio of buffering agent to **PPI** is greater than 40:1, for example at least about 41:1, at least about 42:1, or at least about 43:1. Illustratively, in such an embodiment, the weight ratio of buffering agent to **PPI** will be greater than 40:1 and less than or equal to about 150:1; greater than or equal to about 41:1. . .

DETD . . . of a liquid dosage form. Such compositions can be prepared in any suitable manner, for example by admixing together enteric-coated **PPI** granules (e.g. Prilosec® AstraZeneca) or uncoated **PPI** together with buffering agent, a liquid vehicle, and any other desired excipients (in any order of admixing). In one embodiment, the **PPI** is mixed with a pre-made solution comprising buffering agent to achieve a desired final **PPI** concentration. Illustratively, the concentration of **PPI** in the solution can range from approximately 0.2 mg/ml to about 20 mg/ml, about 0.3 mg/ml to about 15 mg/ml,. . .

DETD . . . action of microorganisms. Additionally, thickening agents such as methylcellulose can be used in order to reduce the settling of the **PPI** in suspension.

DETD [0088] In one embodiment, a liquid **PPI** composition is provided that is stable at room temperature for several weeks and that inhibits the growth of bacteria or. . . shown in Example 10 below. In another embodiment, a liquid composition of the invention maintains greater than 90% of its **PPI** potency for a period of at least 12 months.

DETD . . . In one embodiment, compositions of the invention are in non-enteric coated form. In another embodiment, a first portion of the **PPI** can be enteric coated while a second portion of the **PPI** is non-enteric coated to provide a dual-release system. Such a composition is contemplated where both an immediate and a delayed. . .

DETD . . . onset of therapeutic effect. The term "immediate release" is intended to refer to any composition in which release of the **proton pump inhibitor** occurs relatively quickly after oral administration. In one immediate release embodiment, at least a therapeutically effective amount of **PPI** will be released from such compositions and will be available for absorption (i.e. not degraded) in the gastrointestinal tract.

DETD . . . of a composition of the invention to a subject, at least a therapeutically effective amount of the active ingredient (e.g. **PPI**) is available for absorption in the stomach of the subject. As discussed above, commercially available PPIs require enteric coating to prevent exposure of the **PPI** to gastrointestinal fluids (and consequent drug degradation). Such coatings, however, by preventing release and subsequent absorption of **PPI** in gastrointestinal fluids, lead to delayed therapeutic onset of action. Compositions of the present embodiment, by contrast, do not require. . .

DETD . . . the invention to a human subject, for example a fasted adult human subject, the subject exhibits a plasma T_{max} of **PPI** within about 30 seconds to about 90 minutes, within about 1 minute to about 80 minutes, within about 5 minutes. . .

DETD [0098] In another embodiment, a therapeutically-effective dose of the **PPI** is achieved in the blood serum of a subject at any time within about 10, about 20, about 30 or. . .

DETD [0099] In another embodiment, a therapeutically-effective dose of the **PPI** is achieved in the blood serum of a subject at about 20 minutes to about 12 hours, about 20 minutes. . .

DETD . . . may contain many different variations of the above components. For example, if the tablets or powder are compounded to contain **PPI** and buffering agent, the diluent may be water, sodium bicarbonate, or other compatible diluent, and the dose cup can be. . .

DETD [0103] In another embodiment, the present invention provides a method for enhancing the pharmacologic activity of a **proton pump inhibitor** comprising co-administering with the **PPI** one or more parietel cell activators. The term "co-administer" and derivatives thereof means that the compound can be administered immediately before (e.g. within about 30 minutes and preferably within about 15 minutes), with, or immediately after administration of the **PPI**. The parietal cell activator can be formulated with or separately from the **PPI**.

DETD . . . amount of about 5 mg to 2.5 g per 20 mg dose of omeprazole (or equivalent pharmacologic dose of other **proton pump inhibitor**). The dose of activator administered to a mammal, particularly a human, in the context of the present invention should be sufficient to effect a therapeutic response (i.e., enhanced effect of **proton pump inhibitor**) over a reasonable time frame. The dose will be determined by the strength of the particular compositions employed and the. . .

DETD . . . The approximate effective ranges for various parietal cell activators per 20 mg dose of omeprazole (or equivalent dose of other **proton pump inhibitor**) are:

DETD . . . an irritable bowel syndrome drug, a motility agent, an anti-emetic agent, an alginate, a prokinetic agent, a $H_{2\text{-antagonist}}$, or an **antacid**, which are commonly administered to minimize the pain and/or complications related to this disorder. Illustratively, such drugs include metoclopramide, Lotrenex®,. . .

DETD . . . in which the therapeutic agents are administered is not narrowly critical. "Combination therapy" also can embrace the administration of a **PPI** inhibitor as described herein in further combination with other biologically active agents, including, but not limited to, drugs from the. . .

DETD [0134] Where an **antacid** is desired as part of a combination therapy, the **antacid** can include, but is not limited to, alexitol sodium, almagate, aluminum hydroxide, aluminum magnesium silicate, aluminum phosphate, azulene, basic aluminum. . .

DETD . . . further alternative, sodium bicarbonate powder (about 975 mg per 20 mg dose of omeprazole (or an equipotent amount of other **proton pump inhibitor**) is compounded directly into the tablet. Such tablets are then dissolved in water or sodium bicarbonate 8.4%, or swallowed whole. . . 10 mg

Peppermint	3	mg
Maltodextrin	3	mg
Mannitol	3	mg
Pregelatinized starch	3	mg

B2. 10 mg Tablet Formula.

Proton pump inhibitor: one of the following:		
Omeprazole	10	mg
Lansoprazole	15	mg
Pantoprazole sodium	20	mg
Rabeprazole sodium	10	mg
Other **proton pump inhibitor** in an equipotent amount		
Calcium lactate	375	mg
Calcium glycerophosphate	375	mg
Aspartame calcium (phenylalanine)	0.5	mg
Colloidal silicon dioxide. . .	10	mg
Peppermint	3	mg
Maltodextrin	20	mg
Mannitol	30	mg
Pregelatinized starch	30	mg

B3. 10 mg Tablet Formula.

Proton pump inhibitor: one of the following:

Omeprazole	10	mg
Lansoprazole	15	mg
Pantoprazole sodium	20	mg
Rabeprazole sodium	10	mg
Other **proton pump inhibitor** in an equipotent amount		
Sodium bicarbonate	750	mg
Aspartame sodium (phenylalanine)	0.5	mg
Colloidal silicon dioxide	12	mg
Corn starch. . . 30 mg		
Pregelatinized starch	30	mg

C1. 20 mg Tablet Formula.

Omeprazole or	20	mg (or lansoprazole or pantoprazole other **proton pump inhibitor** in an equipotent amount)
Calcium lactate	175	mg
Calcium glycerophosphate	175	mg
Sodium bicarbonate	250	mg
Aspartame calcium . . 10 mg	0.5	mg
Peppermint	3	mg
Maltodextrin	3	mg
Mannitol	3	mg
Pregelatinized starch	3	mg

C2. 20 mg Tablet Formula.

Proton pump inhibitor: One of the following:

Omeprazole	20	mg
Lansoprazole	30	mg
Pantoprazole	40	mg
Other **proton pump inhibitor** in an equipotent amount		
Calcium lactate	375	mg
Calcium glycerophosphate	375	mg
Aspartame calcium (phenylalanine)	0.5	mg
Colloidal silicon dioxide. . . 10 mg		
Peppermint	3	mg
Maltodextrin	20	mg
Mannitol	30	mg
Pregelatinized starch	30	mg

C3. 20 mg Tablet Formula.

Proton pump inhibitor: One of the following:

Omeprazole	20	mg
Lansoprazole	30	mg
Pantoprazole	40	mg
Other **proton pump inhibitor** in an equipotent amount		
Sodium bicarbonate	750	mg
Aspartame sodium (phenylalanine)	0.5	mg
Colloidal silicon dioxide	12	mg
Corn starch. . . 30 mg		
Pregelatinized starch	30	mg

D1. Tablet for Rapid Dissolution.

Omeprazole or	20	mg (or lansoprazole or pantoprazole other **proton pump inhibitor** in an equipotent amount)
Calcium lactate	175	mg
Calcium glycerophosphate	175	mg
Sodium bicarbonate	500	mg
Calcium hydroxide	50	mg
Croscarmellose sodium	12	mg

D2. Tablet for Rapid Dissolution.

Proton pump inhibitor: One of the following:

Omeprazole	20	mg
Lansoprazole	30	mg
Pantoprazole	40	mg
Rabeprazole sodium	20	mg
Esomeprazole magnesium	20	mg

Other **proton pump inhibitor** in an equipotent amount		
Calcium lactate	300	mg
Calcium glycerophosphate	300	mg
Calcium hydroxide	50	mg
Croscarmellose sodium	12	mg

D3. Tablet for Rapid Dissolution.

Proton pump inhibitor: One of the following:		
Omeprazole	20	mg
Lansoprazole	30	mg
Pantoprazole	40	mg
Rabeprazole sodium	20	mg
Esomeprazole magnesium	20	mg
Other **proton pump inhibitor** in an equipotent amount		
Sodium bicarbonate	700	mg
Trisodium phosphate dodecahydrate	100	mg
Croscarmellose sodium	12	mg

E1. Powder for Reconstitution for Oral Use (or per ng tube).

Omeprazole or	20	mg (or lansoprazole or pantoprazole other **proton pump inhibitor** in an equipotent amount)
Calcium lactate	175	mg
Calcium glycerophosphate	175	mg
Sodium bicarbonate	500	mg
Calcium hydroxide	50	mg
Glycerine	200	mg

E2. Powder for Reconstitution for Oral Use (or per ng tube).

Proton pump inhibitor: One of the following:		
Omeprazole	20	mg
Lansoprazole	30	mg
Pantoprazole	40	mg
Rabeprazole sodium	20	mg
Esomeprazole magnesium	20	mg
Other **proton pump inhibitor** in an equipotent amount		
Calcium lactate	300	mg
Calcium glycerophosphate	300	mg
Calcium hydroxide	50	mg
Glycerine	200	mg

E3. Powder for Reconstitution for Oral Use (or per ng tube).

Proton pump inhibitor: One of the following:		
Omeprazole	20	mg
Lansoprazole	30	mg
Pantoprazole	40	mg
Rabeprazole sodium	20	mg
Esomeprazole magnesium	20	mg
Other **proton pump inhibitor** in an equipotent amount		
Sodium bicarbonate	850	mg
Trisodium phosphate	50	mg

F1. 10 mg Tablet Formula.

Omeprazole	10	mg (or lansoprazole or pantoprazole or other **proton pump inhibitor** in an equipotent at mount)
Calcium lactate	175	mg
Calcium glycerophosphate	175	mg
Sodium bicarbonate	250	mg
Polyethylene glycol	20. . .	Croscarmellose sodium 12 mg
Peppermint	3	mg
Magnesium silicate	1	mg
Magnesium stearate	1	mg

F2. 10 mg Tablet Formula.

Proton pump inhibitor: One of the following:		
Omeprazole	10	mg
Lansoprazole	15	mg
Pantoprazole sodium	20	mg
Rabeprazole sodium	10	mg
Esomeprazole magnesium	10	mg
Other **proton pump inhibitor** in an equipotent amount		
Calcium lactate	475	mg
Calcium glycerophosphate	250	mg

Polyethylene glycol	20	mg
Croscarmellose sodium	12	mg
Peppermint	3	mg
Magnesium silicate	10	mg
Magnesium stearate	10	mg

F3. 10 mg Tablet Formula.

Proton pump inhibitor: One of the following:

Omeprazole	10	mg
Lansoprazole	15	mg
Pantoprazole sodium	20	mg
Rabeprazole sodium	10	mg
Esomeprazole magnesium	10	mg
Other **proton pump inhibitor**	in an equipotent amount	
Sodium bicarbonate	700	mg
Polyethylene glycol	20	mg
Croscarmellose sodium	12	mg
Peppermint	3	mg
Magnesium. . . 10	mg	
Magnesium stearate	10	mg

G1. 10 mg Tablet Formula.

Omeprazole	10	mg (or lansoprazole or pantoprazole or other **proton pump inhibitor** in an equipotent amount)
Calcium lactate	200	mg
Calcium glycerophosphate	200	mg
Sodium bicarbonate	400	mg
Croscarmellose sodium	12	mg
Pregelatinized starch	3	mg

G2. 10 mg Tablet Formula.

Proton pump inhibitor: One of the following:

Omeprazole	10	mg
Lansoprazole	15	mg
Pantoprazole sodium	20	mg
Rabeprazole sodium	10	mg
Esomeprazole magnesium	10	mg
Other **proton pump inhibitor**	in an equipotent amount	
Calcium lactate	400	mg
Calcium glycerophosphate	400	mg
Croscarmellose sodium	12	mg
Pregelatinized starch	3	mg

G3. 10 mg Tablet Formula.

Proton pump inhibitor: One of the following:

Omeprazole	10	mg
Lansoprazole	15	mg
Pantoprazole sodium	20	mg
Rabeprazole sodium	10	mg
Esomeprazole magnesium	10	mg
Other **proton pump inhibitor**	in an equipotent amount	
Sodium bicarboante	750	mg
Croscarmellose sodium	12	mg
Pregelatinized starch	3	mg

DETD [0142] Standard Tablet of **Proton Pump Inhibitor** and Buffering Agent.

DETD [0146] **Proton Pump Inhibitor** Central Core Tablet.

DETD . . . activate the effervescent agents and create the desired solution. In addition, lansoprazole 30 mg (or an equipotent dose of other **proton pump inhibitor**) can be substituted for omeprazole.

DETD . . . patients, 9 were excluded from the study, all based upon insufficient data about commencement, duration or outcome in treatment with **proton pump inhibitor** therapy. This left 24 patients with enough data to draw conclusions.

DETD [0160] Of the 24 remaining patients, 18 were males and 6 females. Ages at implementation of **proton pump inhibitor** therapy ranged from 2 weeks of age to 9 years old. Median age at start of therapy was 26.5 months. . . in a few patients. Six patients had neither pH nor endoscopic documentation of gastroesophageal reflux disease, but were tried on **proton pump inhibitor** therapy based on symptomatology alone.

DETD [0164] The **proton pump inhibitor** suspension used in this group of patients was Choco-Base.TM. suspension of either lansoprazole or omeprazole. The dosing was very uniform,. . .

DETD [0165] Most patients responded favorably to and tolerated the once daily dosing of Choco-Base.TM. **proton pump inhibitor** suspension. Two

patients had documented adverse effects associated with the use of the **proton pump inhibitor** suspension. In one patient, the mother reported increased burping up and dyspepsia, which was thought to be related to treatment. . .

DETD . . . and (4) inconclusive. Of 24 patients with sufficient data for follow up, 18 showed improvement in symptomatology upon commencement of **proton pump inhibitor** therapy [72%]. The seven who did not respond were analyzed and grouped. Three showed no change in symptomatology and clinical. . . 8). Setting aside the cases in which therapy was stopped before conclusions could be drawn and the case in which **proton pump inhibitor** therapy was for purely prophylactic reasons, leaves (17/21) 81 % of patients that responded to Choco-Base.TM. suspension. This means that 19% (4/21) of patients received no apparent benefit from **proton pump inhibitor** therapy. Of all these patients, only 4% complained of worsening symptoms and the side effects were 4% (1/21) and were. . .

DETD . . . a pro-kinetic agent and H-2 blocker therapy. Nonetheless, many patients fail this treatment protocol and become surgical candidates. In adults, **proton pump inhibitor** therapy is effective in 90% of those treated for gastroesophageal reflux disease. As a medical alternative to the H-2 blockers,. . . appropriate dosage should be in this group of patients. A recent review by Israel D., et al. suggests that effective **proton pump inhibitor** dosages should be higher than that originally reported, i.e., from 0.7 mg/kg to 2 or 3 mg/kg omeprazole. Since toxicity. . .

DETD [0170] In the ICU setting, the University of Missouri-Columbia has been using an unflavored **proton pump inhibitor** suspension given once daily per various tubes (nasogastric, g-tube, jejunal feeding tube, duo tube, etc.) for stress ulcer prophylaxis. It. . .

DETD . . . the adult population, but this can be attributed to the refractory nature of their illness, most having failed prior non-**proton pump inhibitor** treatment. The population in this study is not indicative of general practice populations.

DETD [0174] **Proton pump inhibitor** therapy is a beneficial therapeutic option in the treatment of reflux related symptoms in the pediatric population. Its once daily. . .

DETD [0177] In all four of the above formulations, lansoprazole or other **proton pump inhibitor** can be substituted for omeprazole in equipotent amounts. For example, 300 mg of lansoprazole may be substituted for the 200. . .

DETD . . . proton pump and effectively block activated proton pumps (primarily those inserted into the secretory canalicular membrane). By further administering the **proton pump inhibitor** with one of these activators or enhancers, there is a synchronization of activation of the proton pump with the absorption and subsequent parietal cell concentrations of the **proton pump inhibitor**. As illustrated in FIG. 4, this combination produced a much longer pharmacologic effect than when the **proton pump inhibitor** was administered alone.

DETD [0182] Combination Tablet Delivering Bolus And Time-Released Doses of **Proton Pump Inhibitor**

DETD [0248] 1. Currently taking $H_{2\text{-receptor}}$ antagonist, **antacid**, or sucralfate.

DETD [0249] 2. Recent (within 7 days) therapy with lansoprazole, omeprazole, or other **proton pump inhibitor**.

DETD [0262] Intraveneous **Proton Pump Inhibitor** in Combination With Oral Parietal Cell Activator

DETD . . . can be administered either within about 5 minutes before, during or within about 5 minutes after the IV dose of **proton pump inhibitor**.

DETD [0268] Applicant expects that these studies will demonstrate that significantly less IV **proton pump inhibitor** is required to achieve therapeutic effect when it is given in combination with an oral parietal cell activator.

DETD [0269] Additionally, administration kits of IV **proton pump inhibitor** and oral parietal cell activator can be packaged in many various forms for ease of administration and to optimize packing. . .

DETD . . . receiving ketoconazole or itraconazole or enteral tube feedings; or had received an investigational drug within 30 days, omeprazole or another **proton pump inhibitor** within 5 days, or warfarin or nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, within 24 h. Administration of the study drug. . .

DETD [0303] Period 1: 1 **antacid** tablet (30 mEq of 1 part sodium bicarbonate

to 3 parts calcium carbonate) plus 40 mg omeprazole powder was administered. . .

DETD [0306] Period 5: 1 **antacid** tablet (30 mEq of 1 part sodium bicarbonate to 1 part calcium carbonate) plus 40 mg omeprazole powder was administered. . .

DETD . . . the drug product by site staff directly onto the dorsal mid-tongue. Immediately thereafter, subjects were administered one or two chewable **antacid** tablets and began chewing. Each subject continued to chew the tablet(s), while mixing it with the omeprazole powder, carefully avoiding. . .

DETD [0352] The chewable **antacid** tablets were produced by Murty Pharmaceuticals, Inc. (518 Codell Drive, Lexington, Ky. 40509-1016) and contained sodium bicarbonate and calcium carbonate,. . .

DETD [0356] **Proton Pump Inhibitor** Compositions and Method for Optimizing the Buffer to be Administered in Combination with a **Proton Pump Inhibitor**

DETD . . . proton pump inhibiting agents, for example, can be formulated or coadministered with one or more buffers sufficient to protect the **proton pump inhibitor** in any environment, with the ultimate goal being to deliver a **proton pump inhibitor** to the stomach (or other environment) either via a liquid, a powder or solid dosage form that produces an immediate release of active drug to the site of delivery such that the **proton pump inhibitor** is quickly available for absorption. Accordingly, Applicant has found that certain amounts of buffers coadministered or mixed with certain proton pump inhibiting agents prevent acid degradation of the **proton pump inhibitor** when the buffers produce a pH in the stomach or other site of environment that is equal to the pKa of the **proton pump inhibitor** plus an amount sufficient to protect the **proton pump inhibitor** from acids and provide undegraded and bioactive **proton pump inhibitor** to the blood upon administration (e.g., a final pH of pKa of **proton pump inhibitor** +0.7 log value will reduce the degradation to about 10%). Such buffers should interact with hydrogen ion at rates that exceed the interaction of hydrogen ion with the **proton pump inhibitor**. Thus, the solubilities of the buffers and proton pump inhibiting agents are important considerations because solubility is a key determinant. . .

DETD [0359] Typically, a **proton pump inhibitor** formulation of the present invention comprises two primary components: a **proton pump inhibitor** and an Essential Buffer. An Essential Buffer may include a buffer or combination of buffers that interact with HCl (or other acids in the environment of interest) faster than the **proton pump inhibitor** interacts with the same acids. When placed in a liquid phase (usually in water), the Essential Buffer produces and maintains a pH of at least the pKa of the **proton pump inhibitor**. In one embodiment, by raising the pH of the environment to the same of the pKa of the **proton pump inhibitor** plus about 0.7 log value (or greater), the expected degradation (ionization) can be reduced from about 50% to about 10%.. . . pH" is the lowest pH of the environment of interest needed to minimize or eliminate the acid-induced degradation of the **proton pump inhibitor**. The buffering agent(s) employed may raise the pH of the environment to the Essential pH such that 30%, 40% or 50% of the **proton pump inhibitor** is undegraded, or be present in an amount sufficient to substantially protect (i.e., greater than 50% stability) the **proton pump inhibitor**.

DETD [0360] In another embodiment, the Essential pH is the pKa of the **proton pump inhibitor**. In a further embodiment, the Essential pH is the sum of the pKa of the **proton pump inhibitor** plus log 0.7. A log value of about 0.7 is added to the pKa, which represents a decrease of about 5.01187% in stability of the **proton pump inhibitor** from the pKa plus 1 log value, thus resulting in a stability of approximately 90%, a value widely accepted as. . .

DETD . . . (Essential Buffer Capacity ("EBC")) to maintain the elevated pH of the environment (usually gastric) throughout the dwell time that the **proton pump inhibitor** is passed from the environment and into the blood.

DETD . . . the value that leads to tissue irritation or damage and above a lower limit for the Essential pH of the **proton pump inhibitor**. Secondary Essential Buffers are not required in every formulation but can be combined with Primary Essential Buffers to produce a. . .

DETD . . . dose of buffer to protect acid labile substituted benzimidazole proton pump inhibiting agents (and other drugs) is useful for efficacious **proton pump inhibitor** delivery to and action upon parietal cell proton pumps, particularly when the **proton pump**

inhibitor is administered as an immediate release product designed to disintegrate in the stomach rather than a traditional delayed-release product designed. . . the buffer(s) to be used, as well as calculations to determine Essential pH, buffering capacity, and volume measurements for individual **proton pump inhibitor** doses based on their respective solubilities and pKa's. Such inventive methods are applicable for determining the type and amount of buffer(s) necessary to protect the **proton pump inhibitor** in an array of environments (e.g., mouth, esophagus, stomach, duodenum, jejunum, rectal vault, nasogastric tube, or a powder, tablet, capsule,. . .

DETD [0366] The Essential Buffering Capacity ("EBC") is the capacity of a **proton pump inhibitor**/buffer formulation to resist degradation from its environment. The buffering capacity of a **proton pump inhibitor**/buffer formulation is primarily derived from components of the formulation that possess the ability to combine with acids (H+ ions) from the environment. The EBC contributes to both acid neutralization (**antacid** effect) and to maintaining an environmental pH>pKa+0.7 to protect proton pump inhibiting agents from acid degradation throughout the dwell time.. . . (or other environment) at a somewhat constant level within a desired range for a period of time so that the **proton pump inhibitor** can be absorbed from the gastric or other environment. Accordingly, the Essential Buffer is generally more rapid in its complexation with HCl (or other acid) than the **proton pump inhibitor** administered so that the Essential Buffer is capable of protecting the **proton pump inhibitor**.

DETD [0369] Secondary Essential Buffers do not play an important role in protecting the **proton pump inhibitor** from early acid-induced degradation. Because they do not work as rapidly, they do not play a major role in **proton pump inhibitor** protection through the dwell time. Other buffers ("Non-Essential Buffers") can be added to the Primary and/or Secondary Essential Buffers to provide a latent **antacid** effect that extends beyond the **antacid** effect of Essential Buffers.

DETD . . . feeds or other sources. In general, the higher the pH of the gastric environment, the greater the stability of the **proton pump inhibitor**, and thus the more time it has to undergo absorption into the blood and reach and act upon the proton. . .

DETD . . . pH" is the lowest pH of the environment of interest needed to minimize or eliminate the acid-induced degradation of the **proton pump inhibitor** during the dwell time in the environment. It is generally expressed herein as pH range. Such pH is the pH of the environment in which the **proton pump inhibitor**/buffer formulation resides. For example, the environment may be a storage container or the stomach. The environment presents a set of conditions to the **proton pump inhibitor**/buffer, such as temperature, pH, and the presence or absence of water. The dwell time is the time that the **proton pump inhibitor** dwells in a specific environment, i.e., the GI tract prior to its passage into a different environment, i.e. the blood. . . container of dry, powdered formulation. As used herein, "Resultant pH" is the pH that is the result of adding a **proton pump inhibitor**/buffer formulation to an environment of interest. "Formulation pH" is the pH of the **proton pump inhibitor**/buffer formulation when it is in liquid form.

DETD [0379] A **proton pump inhibitor** dose within its calculated pH_E range is designed to ensure sufficient **proton pump inhibitor** protection from acid degradation such that delivery to and action upon proton pumps occur. In one desirable embodiment, the pH_E is the sum of the pKa of a given **proton pump inhibitor** plus about 0.7. The pKa is defined as the pH at which 50% of a chemical is in the ionized form. When the pH of the environment equals the pKa of the **proton pump inhibitor**, then 50% ionization (degradation) of the **proton pump inhibitor** occurs. However, by adding the factor of 0.7, this ionization is reduced to 90%.

DETD . . . is the range of pH elevation in which the lower limit is the sum of the pKa of a given **proton pump inhibitor** +0.7 log, and the upper limit is the pH at which elimination of acid degradation occurs without producing tissue irritation. . .

DETD . . . buffer is an important aspect of the tissue destructive potential of an alkaline substance. Therefore, the SRF for any given **proton pump inhibitor** begins at the sum of the pKa of the **proton pump inhibitor** +0.7, and extends upwards to a pH of about 10.9.

DETD . . . SRF establishes a desirable range for the stability to the actions of H+ ion (or other acidic component) on the **proton pump**

inhibitor/buffer formulation. Sufficient buffering capacity maintains an Essential pH as described below as "Essential Buffering Capacity."

DETD [0384] pH_E of **proton pump inhibitor**=pKa of **proton pump inhibitor**+0.7.

DETD . . . a factor of 10, any local effects within the stomach that may produce areas of lower pH that might cause **proton pump inhibitor** degradation. A value of +1 log value is also supported by the observation that weak bases operate most efficiently at. . .

DETD . . . However, magnesium hydroxide is not rapid in onset and care should be taken to ensure that early degradation of the **proton pump inhibitor** does not occur. Early degradation can be avoided by making a tablet comprising **two layers**: an inner layer of **proton pump inhibitor** and sodium bicarbonate, and an outer layer of magnesium hydroxide dried gel or magnesium oxide with suitable disintegrant such that. . . rapidly disintegrate in the stomach. Alternatively, the inner layer can contain the magnesium buffer and the outer layer has the **proton pump inhibitor** and sodium bicarbonate.

DETD . . . best suited in an outer layer of a tablet formulation with the inner layer comprising a rapid acting buffer with **proton pump inhibitor** (or vice versa). Alternatively, mixtures of the buffers can be employed for the outer layer. If developing a liquid formulation. .

DETD [0397] As mentioned above, the pKa of a given **proton pump inhibitor** indicates inherent stability with respect to acid degradation; the lower the pKa, the more stable the **proton pump inhibitor**. The solubility of the **proton pump inhibitor** will also dictate the rate at which the **proton pump inhibitor** complexes with, and is degraded by, acid. These two physicochemical characteristics (pKa and solubility) of the **proton pump inhibitor** interact with the physicochemical characteristics of the buffer(s) (pH, buffering capacity and rate of buffering action) in the presence of acid in the environment to determine the degradation of the **proton pump inhibitor** over time. The less soluble a **proton pump inhibitor** is in water, the lower the initial degradation when placed in an acidic environment. The following Table 11 elaborates on. . .

DETD . . . overall pH of the gastric contents should be kept at least at the pKa+0.7 (i.e., 3.7) from the time the **proton pump inhibitor** in solution comes into contact with the gastric acid continuing throughout the dwell time. Essential Buffers for liquid formulations of. . .

DETD [0400] Another option for rabeprazole sodium (as well as any sodium salt of a **proton pump inhibitor**, which would tend to be more soluble than the base form) is to reduce the solubility of rabeprazole sodium when. . .

DETD . . . that possess high pKa's, such as rabeprazole sodium, a two-part liquid formulation can be utilized. The liquid part has the **proton pump inhibitor** and a high pH, but a low mEq buffering capacity. The liquid part is added to a second part that. . .

DETD . . . as a tablet, capsule or powder with a buffer(s), which disintegrate and reach solution at a rate that exceeds the **proton pump inhibitor** and thereby provides the Essential pH for protection of the **proton pump inhibitor** prior to its dissolution and interaction with the acid in the environment. Further, the tablet or capsule may be formulated to possess an outer portion of buffer and an inner portion comprising **proton pump inhibitor**, or a blend of **proton pump inhibitor** and buffer. Additional methods include formulating the buffer in a smaller particle size (e.g., micronized) and the **proton pump inhibitor** in a larger particle size. This results in the disintegration of the buffer component prior to disintegration of the **proton pump inhibitor** component. All of these methods of formulation aim to create an environment of stability for the **proton pump inhibitor** during the dwell time.

DETD . . . a buffer that raises the pH of the environment to greater than or equal to the pH_E of a particular **proton pump inhibitor** in a time sufficient to prevent significant degradation of the **proton pump inhibitor**. In one embodiment, the rapid acting buffer raises the pH to at least the pKa of the **proton pump inhibitor** plus 0.7 log value within 10 minutes.

DETD . . . the onset of pH change to equal to or greater than the pH_E+0.7 begins before the acid-induced degradation of the **proton pump inhibitor** occurs, and (2) the Resultant pH at or greater than the pH_E+0.7 lasts throughout the dwell time, which is typically. . . the particle size of the buffer(s) can be reduced to enhance the

dissolution rate while the particle size of the **proton pump inhibitor** can be increased. Disintegrants can be added to enhance the availability of poorly soluble buffers.

DETD . . . pH of the gastric contents (or other environment) should be kept at greater than about 4.8 from the time the **proton pump inhibitor** in solution comes into contact with the gastric acid continuing throughout the dwell time.

DETD . . . that contain a tablet in a tablet, the Essential Buffer complexes with the acid at a faster rate than the **proton pump inhibitor** it is intended to protect.

DETD [0419] When the **proton pump inhibitor**/buffer formulation is placed in the environment, the **proton pump inhibitor** is subject to degradation by the acid in that environment. As depicted in FIG. 9, **proton pump inhibitor** solubility, the pKa of the **proton pump inhibitor**, and the amount and concentration of acid (H+ ion) encountered in the environment are variables that can be used to determine the appropriate candidate as an Essential Buffer. Early degradation occurs when the soluble portion of the **proton pump inhibitor** (that portion available for immediate interaction with H+ ion) undergoes hydrolysis by H+ ion. proton pump inhibiting agents differ in their solubility and, therefore, those that are more soluble have a potential for a higher portion of **proton pump inhibitor** degraded by early interaction with H+ ion. The pKa of the **proton pump inhibitor** and the pH of the environment of the stomach (or other site of interest) after addition of the **proton pump inhibitor**/buffer formulation (Resultant pH) can be used to determine the desirable Essential Buffer. By measuring the Resultant pH over time, the. . .

DETD . . . has been described in part for use in evaluating antacids by Beneyto J E, et. al., Evaluation of a New **Antacid**, Almagate, ARZNEIM-FORSCH/DRUG Res 1984; 34 (10A):1350-4; Kerkhof N J, et al, pH-Stat Tiration of Aluminum Hydroxide Gel, J. PHARM. SCI.. . .

DETD . . . products. In addition, a sample of the test solution can be taken during the experiment to evaluate the extent of **proton pump inhibitor** degradation at various times. Those buffers with a suitable profile as exemplified in FIG. 9 able to maintain pH greater. . .

DETD . . . alkaline buffer, included in the dose and calculated to maintain the Essential pH range and thereby protect any substituted benzimidazole **proton pump inhibitor** in the gastric (or other) environment. In patients requiring continuing **proton pump inhibitor** administration (e.g. daily), more buffering capacity may be necessary with the first dose or first few doses than with subsequent doses because the **proton pump inhibitor** may encounter more acid with the initial doses. Subsequent doses will require less buffering capacity because the initial **proton pump inhibitor** doses will have reduced gastric acid production. The EBC could therefore be reduced in subsequent doses. The product's buffering capacity. . .

DETD [0426] Numerous references are available to assist the skilled artisan in identifying a suitable buffer companion with a **proton pump inhibitor** to determine the desirable characteristics stated herein. See, e.g., Holbert, et. al., A Study of **Antacid** Buffers: I. The Time Factor in Neutralization of Gastric Acidity, J. AMER. PHARM. ASSN. 36: 149-51 (1947); Lin, et. al.,. . .

DETD [0428] The Desirable Volume ("DV") of a **proton pump inhibitor** dose may affect **proton pump inhibitor** delivery to and action upon parietal cell proton pumps. The DV of a dose is partly based on the EBC. For liquid formulations, a desirable volume should deliver sufficient buffer to act as an **antacid** to neutralize a substantial amount of gastric or other acids. For solid formulations such as tablets, a nominal amount of. . .

DETD . . . butterscotch, and peanut butter flavorings, used alone or in any combination. Similarly, all substances included in the formulation of any **proton pump inhibitor** product, including but not limited to, activators, antifoaming agents, potentiators, antioxidants, antimicrobial agents, chelators, sweeteners, thickeners, preservatives, or other additives. . .

DETD [0439] The pH_E, the EBC, and the DV of a **proton pump inhibitor** dose may affect **proton pump inhibitor** delivery to, and action upon, parietal cell proton pumps. The following calculations tailor an Essential Buffer dose for any substituted benzimidazole **proton pump inhibitor** to promote **proton pump inhibitor** efficacy in an oral administration.

DETD . . . order to enhance the shelf-life, higher pH values would be anticipated within the range of acceptable pH_E for a given **proton pump inhibitor**. As an example, rabeprazole suspensions containing various buffers were evaluated for color change because degradation of proton pump inhibiting agents. . .

DETD [0479] Similar calculations may be performed for any substituted benzimidazole **proton pump inhibitor** and appropriate buffer(s) including, but not limited to, those exemplified above. One skilled in the art will appreciate that the. . . above steps is not critical to the invention. The above calculations may be used for formulations comprising one or more **proton pump inhibitor** and one or more buffers.

DETD . . . mEq.

Formulation 5: Veterinary Formulation of Omeprazole

This formulation is particularly well suited for animals rather than humans because the dose of **proton pump inhibitor** is high.

EBC = 75 mEq

Essential pH (omeprazole pKa = 3.9 + 0.7 ≥ 4.6)

Proton pump inhibitor:	500	mg (a range of
Omeprazole powder		350 to 700 mg)
Primary Essential Buffer(s):		
Sodium bicarbonate	5	g (59.5 mEq)
Dibasic sodium phosphate	2.	. . Any Secondary Essential

Buffer(s) may be added in higher or lower amounts to adjust pH for desired stability and additive **antacid** or buffering effect.)

DETD . . .

Formulation 6: Veterinary Formulation of Lansoprazole

Essential pH (lansoprazole pKa = 4.1 + 0.7 ≥ 4.8)

EBC = 71.4 mEq

Proton pump inhibitor:	750	mg
Lansoprazole powder		
Primary Essential Buffer(s):		
Sodium bicarbonate	6	g (71.4 mEq)

(* Any Secondary Essential Buffer(s) may be added in higher or lower amounts to adjust pH for desired stability and additive **antacid** or buffering effect.)

DETD . . .

Formulation 7: Veterinary Formulation of Lansoprazole

Essential pH (lansoprazole pKa = 4.1 + 0.7 ≥ 4.8)

EBC = 63.3 mEq

Proton pump inhibitor:		
Lansoprazole powder	750	mg
Primary Essential Buffer(s)		
Sodium bicarbonate	5	g (59.5 mEq)
Secondary Essential Buffer(s):		
Sodium carbonate	400	mg* (3.8 mEq)

(*Any Secondary Essential Buffer(s) may be added to adjust pH for desired stability and additive **antacid** or buffering effect.)

DETD . . .

Formulation 8: Veterinary Formulation of Esomeprazole Magnesium

Essential pH (esomeprazole pKa = 3.9 + 0.7 ≥ 4.6)

EBC = 53.2 mEq

Proton pump inhibitor:		
Esomeprazole magnesium powder	500	mg

Primary Essential Buffer(s):
Sodium bicarbonate 5 g (47.6 mEq)
Dibasic sodium phosphate 800 mg. . . Any Secondary Essential Buffer(s) may be added in higher or lower amounts to adjust pH for desired stability and additive **antacid** or buffering capacity.)
DETD . . . mEq)

(*Any Secondary Essential Buffer(s) may be added in higher or lower amounts to adjust pH for desired stability and additive **antacid** or buffering capacity.)
DETD . . . may be added to achieve esomeprazole concentrations ranging from 0.2 to 20 mg/mL.

Formulation 10: Veterinary Formulation: Buffer Base .TM. Without **Proton Pump Inhibitor**

EBC = 71.4 mEq
Primary Essential Buffer:
Sodium bicarbonate 6 g 71.4 mEq
Optional Secondary Essential Buffer:
Tribasic sodium. . . mg*

(*Any Secondary Essential Buffer may be added in higher or lower amounts to adjust pH for desired stability and additive **antacid** or buffering capacity.)
DETD . . . butterscotch flavor 100 mg, thaumatin powder 5 mg, and sucrose 30 Gm. Q.s. to 100 mL with distilled water. A **proton pump inhibitor** or other acid-labile drug may be added by the compounding pharmacist selected from available proton pump inhibiting agents or acid-labile drugs from powder or enteric-coated oral solid dosage forms. Different volumes of water may be added to achieve **proton pump inhibitor** concentrations ranging from 0.8 to 20 mg/mL. If other acid labile drugs are employed, the range of concentrations would be. . .
DETD . . . Essential Buffer may range from about 4 mEq to about 30 mEq per dose.

Formulation 11: Oral Buffer Complex Without **Proton Pump Inhibitor** (for general use to protect acid labile drugs) Multidose Composition

Primary Essential Buffer:
Dibasic sodium phosphate or 10 g
sodium. . . Any Secondary Essential Buffer may be added in higher or lower amounts to adjust pH for desired stability and additive **antacid** or buffering capacity.)
DETD . . . maple, butter pecan and other flavorings as have been outlined previously. Different volumes of water may be added to achieve **proton pump inhibitor** concentrations ranging from 0.8 to 20 mg/mL.
DETD [0497] Weigh out approximately 60 g of the formulation. Add **proton pump inhibitor** (or other acid-labile drug) typically in the amount equivalent to 10 doses (range 1 dose to 30 doses). Q.s. to 100 mL with distilled water.

Formulation 12: Oral Buffer Complex Without **Proton Pump Inhibitor** For General Use to Protect Acid Labile Drugs; Protein Free, Multi-Dose Example

Primary Essential Buffer:
Sodium bicarbonate 5 g
(range. . . mg

(*Any Secondary Essential Buffer may be added in higher or lower amounts to adjust pH for desired stability and additive **antacid** or buffering capacity.)
Note that cocoa is a parietal cell activator.
DETD . . . protected from light and moisture, such as in a foil packet.

Weigh out approximately 60 g of the formulation. Add **proton pump inhibitor** (or other acid-labile drug) typically in the amount equivalent to 10 doses (range=1 dose to 30 doses).

DETD [0499] Q.s. to 100 mL with distilled water. Different volumes of water may be added to achieve **proton pump inhibitor** concentrations ranging from 0.8 to 20 mg/mL.

Formulation 13: Buffer Complex Without **Proton Pump Inhibitor** For General Use to Protect Acid Labile Drugs; Protein Free, Lactose Free Multidose Example

Proton pump inhibitor:
None (to be added later, e.g. by compounding pharmacist)
Primary Essential Buffer(s):
Sodium bicarbonate 8 g (range 2 g. . .

DETD [0501] Weigh out approximately 60 g of the formulation. Add **proton pump inhibitor** (or other acid-labile drug) typically in the amount equivalent to 10 doses (range=1 dose to 30 doses). Q.s. to 100 mL with distilled water. Different volumes of water may be added to achieve **proton pump inhibitor** concentrations ranging from 0.3 to 20 mg/mL.

Formulation 14: Buffer Complex Without **Proton Pump Inhibitor** For General Use to Protect Acid Labile Drugs; Protein Free, Multi-Dose Example

Proton pump inhibitor:
None (to be added later, e.g. by compounding pharmacist)
Primary Essential Buffer(s):
Dibasic sodium phosphate 8 g (range 2. . .

DETD [0503] Weigh out approximately 60 g of the formulation. Add **proton pump inhibitor** (or other acid-labile drug) typically in the amount equivalent to 10 doses (range=1 dose to 30 doses). Q.s. to 100 mL with distilled water. Different volumes of water may be added to achieve **proton pump inhibitor** concentrations ranging from 0.8 to 20 mg/mL.

Formulation 15: Buffer Complex Without **Proton Pump Inhibitor** For General Use to Protect Acid Labile Drugs; Protein Free, Multi-Dose Example

Proton pump inhibitor:
None (to be added later, e.g. by compounding pharmacist)
Primary Essential Buffer(s):
Sodium bicarbonate 8 g (range 1 g. . .

DETD . . . protected from light and moisture, such as in a foil packet. Weigh out approximately 60 g of the formulation. Add **proton pump inhibitor** (or other acid-labile drug) typically in the amount equivalent to 10 doses (range=1 dose to 30 doses). Q.s. to 100 mL with distilled water. Different volumes of water may be added to achieve **proton pump inhibitor** concentrations ranging from 0.8 to 20 mg/mL.

Formulation 16: One Phase Lansoprazole 30 mg Tablet

Lansoprazole has a pKa of 4.1;. . . include, but are not limited to, sodium bicarbonate, sodium carbonate, dibasic sodium phosphate, and dipotassium phosphate.
Enough powder for 11 tablets is weighed out:
Proton pump inhibitor:
Lansoprazole powder 330 mg

Primary Essential Buffer(s):
Sodium bicarbonate USP 5500 mg
Dibasic sodium phosphate 2200 mg
DETD . . . not limited to, sodium bicarbonate, sodium carbonate, disodium hydrogen phosphate (dibasic sodium phosphate), and dipotassium phosphate.
Enough powder for 11 tablets is weighed out:
Proton pump inhibitor:
Omeprazole powder USP 220 mg
Primary Essential Buffer(s):
Sodium bicarbonate USP 6500 mg
Magnesium oxide powder 1650 mg
Croscarmelose sodium 300 mg
DETD . . . also be added.

Formulation 18: One Phase Omeprazole 40 mg Tablet

Enough powder for 11 tablets is weighed out:
Proton pump inhibitor:
Omeprazole powder USP 440 mg
Primary Essential Buffer(s):
Sodium bicarbonate USP 6500 mg
Magnesium oxide 1650 mg
. . .
DETD . . . as croscarmelose sodium and glidants such as magnesium stearate may additionally be used.

Formulation 19: Omeprazole Powder Formulations (single dose)

Proton pump inhibitor:
Omeprazole powder USP 20 mg or
(or esomeprazole magnesium). 40 mg
Primary Essential Buffer(s):
Sodium bicarbonate USP powder (60. . .
DETD . . . with 5 mL to 20 mL distilled water at the time of use.

Formulation 23: Flavored Lansoprazole Powder (single dose)

Proton pump inhibitor:
Lansoprazole powder USP 30 mg
Primary Essential Buffer(s):
Dibasic Sodium Phosphate USP or 1500 mg
Sodium bicarbonate USP
Sucrose. . .
DETD . . . with 5 mL to 20 mL distilled water at the time of use.

Formulation 24: Unflavored Rabeprazole Powder (single dose)

Proton pump inhibitor:
Rabeprazole sodium powder USP 20 mg
Primary Essential Buffer(s):
Disodium phosphate duohydrate USP 2000 mg
Optional Secondary Essential. . .
DETD . . . rabeprazole sodium. This causes the rabeprazole sodium to remain insoluble thereby increasing its stability.

Formulation 25: Unflavored Rabeprazole Powder (single dose)

Proton pump inhibitor:
Rabeprazole sodium powder USP 20 mg
Primary Essential Buffer(s):
Sodium bicarbonate USP 1200 mg

Secondary Essential Buffer(s):
Trisodium phosphate USP 300 mg
Optional. . . Buffer(s):
Sodium hydroxide or Tribasic potassium may be added in higher or lower amounts to adjust pH for desired stability and additive **antacid** or buffering capacity.
DETD . . . formulation is designed to enable the use of the commercially available enteric-coated tablet of rabeprazole as the source of the **proton pump inhibitor**. This tablet requires disintegration prior to use as a liquid formulation. Part 1 (the low concentration of Secondary Essential Buffer). . . and simply added to the Primary Essential Buffer(s) (part 2) prior to use.

Formulation 26: Unflavored Rabeprazole Powder (single dose)

Proton pump inhibitor:
Rabeprazole sodium powder USP 20 mg
Primary Essential Buffer(s):
Calcium lactate USP 700 mg
Calcium glycerophosphate 700 mg. . .
DETD . . . dissolving rabeprazole sodium delayed-release tablets (if used as a source of rabeprazole sodium).

Formulation 27: Unflavored Esomeprazole Powder (single dose)

Proton pump inhibitor:
Esomeprazole magnesium powder USP 20 mg
Primary Essential Buffer(s):
Calcium lactate USP 800 mg
Calcium glycerophosphate 800 mg. . .
DETD . . . a source of esomeprazole magnesium).

Formulation 28: Omeprazole Two Part Tablet

Two part tablets contain an outer buffer phase and inner buffer/ **Proton pump inhibitor** core. Enough for 6 tablets is weighed out.
Inner Core:
Proton pump inhibitor:
Omeprazole powder USP 120 mg
(or esomeprazole magnesium or omeprazole sodium).
Primary Essential Buffer(s):
Sodium bicarbonate USP 1200 mg
Outer Phase:
Sodium bicarbonate USP 3960 mg

(Secondary. . .
DETD [0524] The outside layer surrounding the **proton pump inhibitor** tablet serves as a pH-buffering zone. Enough sodium bicarbonate for 6 tablets is weighed out with approximately 280 mg per. . .
DETD . . . bicarbonate and magnesium oxide.

Formulation 29: Lansoprazole Two Part Tablet

Enough for 6 tablets is weighed out.
Inner Core:
Proton pump inhibitor:
Lansoprazole powder USP 180 mg
Primary Essential Buffer:
Sodium bicarbonate USP 1200 mg
Outer Phase:
Sodium bicarbonate USP 3960 mg
DETD . . . starch may be added.

Formulation 30: Pantoprazole Two Part Tablet

Enough for 6 tablets is weighed out.
Inner Core:
Proton pump inhibitor:

Pantoprazole powder USP (or pantoprazole sodium)	240	mg
Primary Essential Buffer:		
Sodium bicarbonate USP	1200	mg

Outer Phase:
Sodium bicarbonate. . .
DETD . . . be added.

Formulation 31: Omeprazole or esomeprazole two part tablet.

Enough for 6 tablets is weighed out.
Inner Core:
Proton pump inhibitor:

Omeprazole powder USP (or esomeprazole or omeprazole sodium).	120	mg
Primary Essential Buffer:		
Sodium bicarbonate	1200	mg

Outer Phase:
Sodium. . .
DETD . . . to enhance neutralization capacity.

Formulation 32: Lansoprazole Two part tablet

Enough for 6 tablets is weighed out.
Inner Core:
Proton pump inhibitor:

Lansoprazole powder USP	180	mg
Primary Essential Buffer:		
Sodium bicarbonate	1200	mg
Outer Phase:		
Sodium bicarbonate	3960	mg

DETD . . . to enhance neutralization capacity.

Formulation 33: Pantoprazole Two part tablet

Enough for 6 tablets is weighed out.
Inner Core:
Proton pump inhibitor:

Pantoprazole sodium powder USP	240	mg
Primary Essential Buffer:		
Sodium bicarbonate	1200	mg
Outer Phase:		
Sodium bicarbonate	3960	mg

DETD . . . carbonate or others, may be added to enhance neutralization capacity.

Formulation 34: Omeprazole 20 mg Two-Part Tablet

Inner Core:
Proton pump inhibitor:

Omeprazole enteric coated granules (base, or sodium salt or esomeprazole sodium or magnesium)	20	mg
Outer Phase:		
Sodium bicarbonate powder. . .		

DETD . . . the inner core as described in Formulation 28. Other variations of this tablet include a uniform enteric coating surrounding the **proton pump inhibitor** of the inner core instead of separate enteric coated granules.

Formulation 35: Lansoprazole 30 mg Two-Part Tablet

Inner Core:
Proton pump inhibitor:
Lansoprazole enteric coated granules 30 mg
Outer Phase:
Sodium bicarbonate powder USP 1000 mg

DETD [0533] This two-part tablet is formulated as per Formulation 34.

Formulation 36: Rabeprazole 20 mg Two-Part Tablet

Inner Core:
Proton pump inhibitor:
Rabeprazole enteric coated granules 20 mg
Outer Phase:
Sodium bicarbonate powder USP 1000 mg

DETD . . . as in Formulation 28. The outer phase is combined with the inner core as in Formulation 28.

Formulation 38: Combination **Antacid** and Enteric Coated Dosage Form

Omeprazole enteric coated granules or enteric coated tablet	20	mg (or an equivalent dose of another **proton pump inhibitor**)
Calcium carbonate	1000	mg

DETD . . . in either a compressed tablet or in a larger capsule. In another embodiment, a capsule containing enteric coated granules of **proton pump inhibitor** can be placed within a larger capsule containing the calcium carbonate.

DETD . . . aluminum salts) because in many cases, sodium bicarbonate more quickly lowers gastric pH.

Formulation 39: Combination Rapid Release and Delayed Released **Proton Pump Inhibitor** and **Antacid**

Inner core:

Omeprazole enteric coated granules or enteric coated tablet	10 or 20	mg (or an equivalent dose of another **proton pump inhibitor**)
Outer phase:		
Omeprazole powder	10 or 20	mg (or equivalent dose of another **proton pump inhibitor**)
Calcium Carbonate powder	1000	mg

DETD [0539] Formulation 40: Soft Chewable **Proton Pump Inhibitor**-Buffer Dosage Form

DETD [0540] Omeprazole 10 or 20 mg (or an equivalent dose of another **proton pump inhibitor**) is combined with the ingredients of a soft chewable **antacid** tablet (e.g., Viactiv®), which comprises calcium carbonate 500 or 1000 mg, corn syrup, sugar, chocolate non fat milk, cocoa butter,. . .

CLM What is claimed is:

. . . An orally deliverable pharmaceutical composition comprising: (a) a therapeutically effective amount of at least one acid labile, substituted benzimidazole H+,K+-ATPase **proton pump inhibitor**; and (b) at least one buffering agent in a total amount greater than 10 mEq; wherein: (i) the composition comprises. . . 3. The composition of claim 1 wherein the at least one **proton pump inhibitor** is selected from the group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, leminoprazole, tenatoprazole, nepaprazole or an enantiomer, isomer,. . .

4. The composition of claim 1 wherein the at least one **proton pump**

inhibitor is present in the composition in a total amount of about 1 mg to about 1000 mg.

5. The composition of claim 1 wherein the at least one **proton pump inhibitor** is present in the composition in a total amount of about 10 mg to about 100 mg.

6. The composition of claim 1 wherein the at least one **proton pump inhibitor** is omeprazole, lansoprazole, or esomeprazole, or an enantiomer, isomer, tautomer, ester, amide, derivative, prodrug, free base, or salt thereof.

16. The composition of claim 1 wherein the at least one **proton pump inhibitor** is present in the composition in a total amount of about 20 to about 40 mg and the at least. . .
17. The composition of claim 1 wherein the at least one **proton pump inhibitor** is present in the composition in a total amount of about 20 to about 40 mg and the at least. . .
18. The composition of claim 1 wherein the at least one **proton pump inhibitor** is present in the composition in a total amount of about 20 to about 40 mg and the at least. . .
. . . An orally deliverable pharmaceutical composition comprising: (a) a therapeutically effective amount of at least one acid labile, substituted benzimidazole H+,K+-ATPase **proton pump inhibitor**; and (b) a combination of at least two non-amino acid buffering agents; wherein: (i) the combination of at least two. . .
24. The composition of claim 23 wherein the at least one **proton pump inhibitor** is selected from the group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, leminoprazole, tenatoprazole, nepaprazole or an enantiomer, isomer,. .
.
25. The composition of claim 23 wherein the at least one **proton pump inhibitor** is present in the composition in a total amount of about 10 mg to about 100 mg.

26. The composition of claim 23 wherein the at least one **proton pump inhibitor** is omeprazole, lansoprazole, or esomeprazole, or an enantiomer, isomer, tautomer, ester, amide, derivative, prodrug, free base, or salt thereof.

35. The composition of claim 23 wherein the at least one **proton pump inhibitor** is present in the composition in a total amount of about 20 to about 40 mg and the at least. . .
36. The composition of claim 23 wherein the at least one **proton pump inhibitor** is present in the composition in a total amount of about 20 to about 40 mg and the at least. . .
37. The composition of claim 23 wherein the at least one **proton pump inhibitor** is present in the composition in a total amount of about 20 to about 40 mg and the at least. . .
. . . An orally deliverable pharmaceutical composition comprising: (a) a therapeutically effective amount of at least one acid labile, substituted benzimidazole H+,K+-ATPase **proton pump inhibitor** in a total amount of about 10 to about 40 mg; and (b) at least one non-amino acid buffering agent;. . .
42. The composition of claim 41 wherein the at least one **proton pump inhibitor** is selected from the group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, leminoprazole, tenatoprazole, nepaprazole or an enantiomer, isomer,. .
.
43. The composition of claim 41 wherein the at least one **proton pump inhibitor** is present in the composition in a total amount of about 10 mg to about 100 mg.

44. The composition of claim 41 wherein the at least one **proton pump inhibitor** is omeprazole, lansoprazole, or esomeprazole, or an enantiomer, isomer, tautomer, ester, amide, derivative, prodrug, free base, or salt thereof.

. . . An orally deliverable pharmaceutical composition comprising: (a) a therapeutically effective amount of at least one acid labile, substituted benzimidazole H+,K+-ATPase **proton pump inhibitor**; and (b) at least one buffering agent in a total amount

greater than 10 mEq; wherein: (i) the composition comprises. . . agent is present, at least one of the following conditions is met: (1) the weight ratio of amino acid buffering agent:**proton pump inhibitor** is greater than 20:1; (2) the composition comprises at least two non-amino acid buffering agents; (3) the composition comprises at least one non-amino acid buffering agent wherein the weight ratio of the at least one non-amino acid buffering agent:**proton pump inhibitor** is greater than 20: 1; and/or (4) the weight ratio of total buffering agent:**proton pump inhibitor** is greater than 40:1. . . . to the subject a composition comprising: (a) a therapeutically effective amount of at least one acid labile, substituted benzimidazole H+,K+-ATPase **proton pump inhibitor**; and (b) at least one buffering agent in a total amount greater than 10 mEq; wherein: (i) the composition comprises. . .

L20 ANSWER 11 OF 31 USPATFULL on STN
Full Text
AN 2004:314007 USPATFULL
TI **Multilayer** orodispersible tablet
IN Oury, Pascal, Le Chesnay, FRANCE
Lamoureux, Gael, Le Boullay Thierry, FRANCE
Herry, Catherine, Marcilly sur Eure, FRANCE
Prevost, Yann, Tremblay Les Villages, FRANCE
PI US 2004247677 A1 20041209
TI **Multilayer** orodispersible tablet
AB The present invention relates to a **multilayer** orodispersible tablet and to the process for preparing it.
SUMM [0001] The present invention relates to a **multilayer** orodispersible tablet and to the process for preparing it.
SUMM [0018] In order to reduce these risks of incompatibility, solutions have been proposed, especially via the preparation of **multilayer** tablets. Such tablets have been described for many years (Abrege de Pharmacie Galenique [Abstract of Pharmaceutical Pharmacy], Le Hir, 3rd. . .
SUMM [0019] They are formed from at least **two layers** that adhere together via a surface.
SUMM [0023] Furthermore, the preparation of a **multilayer** tablet makes it necessary to repeat the application of compression forces on each powder mixture.
SUMM . . . This is why, at the present time, among the solid forms intended to be disintegrated in the mouth, the only **multilayer** tablets that exist are in the form of tablets or pastilles for sucking, for the administration of active substances with. . .
SUMM [0027] These **multilayer** tablets for sucking have a high level of hardness to ensure adhesion of the layers, and have a residence time. . .
SUMM [0031] The Applicant has found, against all expectations, that it is possible to obtain a **multilayer** orodispersible tablet.
DETD . . . relates to a tablet that is orodispersible and that consists of at least two superimposed and integral layers, the said **two layers** each comprising at least one active substance.
DETD [0037] In a first variant of the invention, the orodispersible tablet is a **bi-layer** tablet comprising at least one active substance in each layer.
DETD [0040] Advantageously, the layer containing only excipients is inserted between the **two -layers** each comprising at least one active substance. According to one variant of the invention, the active substance of two of. . .
DETD [0051] The **multilayer** orodispersible tablet according to the invention is particularly suitable for administering medicinal products in combination since it makes it possible. . .
DETD [0055] In the antiulcer field, the preferred combinations combine antiulcer agents, for example a **proton pump inhibitor** such as omeprazole or lansoprazole, an H-2 receptor inhibitor such as famotidine or ranitidine, or an **antacid**.
DETD [0130] The invention also relates to the process for preparing the **multilayer** tablets described above.
DETD [0140] In the case of a **bi-layer** tablet, the process in accordance with the invention comprises the following steps:
DETD [0168] The hardness of the **multilayer** tablet is adapted so as to obtain a friability, measured according to the method of the European Pharmacopoeia, of less. . .
DETD . . . may be used in twin-outlet mode during a high-speed compression

of monolayer tablets or in single-outlet mode during manufacture of **bi-layer** tablets.

DETD . . . may be used in twin-outlet mode during a high-speed compression of monolayer tablets or in single-outlet mode during manufacture of **bi-layer** tablets.

DETD [0196] A precompression of 2.3 kN is applied, before the final compression of the **two layers** successively formed, under a force of 15.3 kN, to target a hardness of 50 to 60 N.

DETD [0198] The **bi-layer** tablets thus prepared have a theoretical mass of 1 400 mg and contain a 500 mg dose of paracetamol and. . .

DETD **Bi-Layer** Orodispersible Tablet Containing 325 mg of Paracetamol and 37.5 mg of Tramadol Hydrochloride (Tramadol HCl)

DETD [0201] A batch of 14 000 **bi-layer** tablets is prepared in the following manner.

DETD [0212] A precompression force of 0.8 kN is applied, before the final compression of the **two layers** successively formed, under a force of 10 kN, to target a hardness of 50 N.

DETD **Bi-Layer** Orodispersible Tablet Containing 200 mg of, Ibuprofen and 37.5 mg of Tramadol Hydrochloride (Tramadol HCl)

DETD [0215] A batch of 14 000 **bi-layer** tablets is prepared in the following manner.

DETD [0225] A precompression force of 0.8 kN is applied, before the final compression of the **two layers** successively formed under a compression force of 10 to 12 kN, to target a hardness of 50 N.

DETD **Bi-Layer** Orodispersible Tablet Containing 500 mg of Paracetamol and 65 mg of Caffeine

DETD [0237] A precompression of 11.2 kN is applied, before the final compression of the **two layers** successively formed, under a force of 33.4 kN- to target a hardness of 70 N.

DETD [0239] The **bi-layer** tablets thus prepared have a theoretical mass of 1 400 mg and contain a 500 mg dose of paracetamol and. . .

DETD **Bi-Layer** Orodispersible Tablet Containing 325 mg of Paracetamol and 37.5 mg of Tramadol Hydrochloride (Tramadol HCl)

DETD [0250] A precompression force of 13.0 kN is applied, before the final compression of the **two layers** successively formed, under a force of 37.1 kN, to target a hardness of 70 N.

DETD [0252] The **bi-layer** tablets thus prepared have a theoretical mass of 1 000 mg and contain a 325 mg dose of paracetamol and. . .

L20 ANSWER 15 OF 31 USPATFULL on STN

Full Text

AN 2004:171513 USPATFULL

TI Gastric acid secretion inhibiting composition

IN Petterson, Anders, Kode, SWEDEN

PI US 2004131674 A1 20040708

AB An oral pharmaceutical dosage form comprises pharmacologically effective amounts of an acid susceptible **proton pump inhibitor** or a salt thereof, an H2 receptor antagonist or a salt thereof and a pharmaceutically acceptable carrier. The dosage form. . .

SUMM [0006] **Antacid** agents, that is, acid neutralizing agents, and alginates are the first therapeutic choice in the treatment of mild heartburn. They have a extremely short duration of action but are seen as inexpensive and safe. **Antacid** agents work locally through a neutralization of gastric acid. Alginates provide some mechanical protection against reflux of gastric acid into the esophagus. The main advantages of **antacid** agents and alginates are, that they provide fast relief of symptoms. The main disadvantage of **antacid** agents and alginates is the extremely short duration of action and dosing has to be repeated frequently to keep the. . .

SUMM [0008] Various combinations of **antacid** and/or mucosa protecting agents with agents that reduce acid secretion have been disclosed to be useful in treating dyspepsia.

SUMM [0010] EP 338861 A describes a solid pharmaceutical preparation consisting of an **antacid** and excipients which is proposed to be used in combination with an acid susceptible **proton pump inhibitor** or any other substance inhibiting gastric acid secretion. There is no suggestion to combine these substances in a fixed unit. . .

SUMM [0011] U.S. Pat. No. 5,244,670 A describes an ingestible pharmaceutical composition comprising a substance selected from the group consisting of **antacid** agents, acid secretion prevention agents, bismuth-containing agents and their mixtures, and 3-(1-menthoxy)-propane-1,2-diol which is present to provide a cooling sensation. . .

SUMM [0012] WO 97/25066 discloses a pharmaceutical formulation comprising a combination of an acid susceptible **proton pump inhibitor** or an H2 receptor antagonist and one or more **antacid** agents or alginates.

SUMM [0021] According to the invention, by combining an H2-receptor antagonist with an acid susceptible **proton pump inhibitor**, it is possible to obtain rapid onset of action as well as good long-term efficacy.

SUMM . . . Thus, according to the invention, is provided an oral pharmaceutical dosage form comprising pharmacologically effective amounts of an acid susceptible **proton pump inhibitor** or a salt thereof, and an H2 receptor antagonist or a salt thereof, and a pharmaceutically acceptable carrier. The terms "**proton pump inhibitor**" and "H2 receptor antagonist" include their isomers, such as enantiomers of proton pump inhibitors, as well as pharmaceutically acceptable salts. . .

SUMM . . . H2 receptor antagonist in an amount effective to reduce the acidity in the stomach after administration and an acid susceptible **proton pump inhibitor** in an amount effective to sustain the low acidity effected by the H2 receptor antagonist over an extended period of. . .

SUMM . . . 6 hours. Acid susceptible proton pump inhibitors are rapidly taking market share from H2 receptor antagonists. The term "acid susceptible **proton pump inhibitor**(s)", as used herein, comprises benzimidazole derivatives having substantial H+,K+-ATPase inhibiting activity, in particular omeprazole, pantoprazole, lanzoprazole, rabeprazole, pariprazole, leminoprazole and. . .

SUMM . . . 1 mg to 100 mg, more preferred from 5 mg to 50 mg, per single dose of an acid susceptible **proton pump inhibitor** or a salt thereof. Preferably the acid susceptible **proton pump inhibitor** or salt thereof is separated from the H2 receptor antagonist by an enteric coating.

SUMM [0028] According to a fourth preferred aspect of the invention the H2 receptor antagonist and the acid susceptible **proton pump inhibitor** need not to be comprised by the same pharmaceutical composition but may be administered separately but within a narrow time. . . interval of 10 min. Thus is disclosed a corresponding dose regimen for separate but joint administration of an acid susceptible **proton pump inhibitor** and an H2 receptor antagonist to treat a condition related to gastric acid secretion.

SUMM [0029] The oral dosage form of the invention thus comprises an acid susceptible **proton pump inhibitor**, an H2 receptor antagonist and a pharmaceutical carrier and, optionally, a gastric acid suppressing agent and/or an alginate. Preferably, the dosage form of the invention comprises from 100 mg to 1000 mg of **antacid** agent and/or alginate. The **antacid** agent of the invention comprises one or several of aluminum hydroxide, calcium carbonate, magnesium carbonate, basic magnesium carbonate, magnesium hydroxide,. . .

SUMM [0030] According to a fifth preferred aspect of the invention the bioavailability of the acid susceptible **proton pump inhibitor** is improved for the first three consecutive doses of a dose regimen or composition of the invention in the treatment of dyspepsia, in particular the first five consecutive doses, since less **proton pump inhibitor** will be degraded during passage of the drug through the stomach.

SUMM [0032] The oral dosage forms of WO 97/25066 comprise an acid susceptible **proton pump inhibitor** in an amount similar or identical to that used in the composition of the present invention, and one or several **antacid** agents and/or alginate(s). The adaptation of the compositions of WO 97/25066 essentially consists in substituting a pharmacologically effective amount of an H2 receptor antagonist for a portion of or the entire amount of the **antacid** agent(s) and/or alginate.

SUMM [0033] According to the invention is provided an oral, multiple unit tableted dosage form comprising an acid susceptible **proton pump inhibitor** in individually enteric coating layered units in combination with an H2 receptor antagonist in the form of a powder or granules compressed into a tablet. The enteric coating layer(s) covering the individual units of the acid susceptible **proton pump inhibitor** has properties such that the compression of the units into a tablet does not significantly affect the acid resistance of. . .

SUMM . . . and easy to handle. Such a multiple unit tableted dosage form comprises enteric coating layered pellets of an acid susceptible **proton pump inhibitor** compacted with a pulverous H2-antagonist.

This dosage form may also contain effervescent components for making it rapidly disintegrate when put. . .

SUMM [0035] According to the invention is also provided a tablet preparation comprising an acid susceptible **proton pump inhibitor** in admixture with tablet excipients forming a tablet core which is enterically coated, and a separate layer surrounding the tablet. . . layers, each one comprising different active substances. One of the layers, preferably the innermost layer (core), comprises the acid susceptible **proton pump inhibitor** in the form of enteric coating layered pellets in admixture with pharmaceutical excipients and the other layer(s) comprise(s) the histamine H2-antagonist(s), respectively in admixture with pharmaceutical excipient(s). Optionally the **two layers** are separated by a separating layer to prevent tacking between the **two layers**. The core comprising the acid susceptible **proton pump inhibitor** may also be advantageously coated directly with an enteric layer by following, for instance, procedures disclosed in WO 00/78284 which. . .

SUMM [0036] According to the invention the acid susceptible **proton pump inhibitor** in the form of enteric coating layered pellets may be mixed with histamine H2-antagonist(s) and optionally pharmaceutical excipient(s) to be. . .

SUMM [0037] It is thus preferred for the dosage form of the invention to comprise the acid susceptible **proton pump inhibitor** or a salt thereof protected by an enteric coating layer and, optionally, a layer separating it from the enteric coating.. . . the invention comprises two concentric layers optionally separated by one or more separating layer(s), one layer comprising said acid susceptible **proton pump inhibitor** or salt thereof, the other layer comprising said H2 receptor antagonist or salt thereof. The inner layer comprises the acid susceptible **proton pump inhibitor** or salt thereof and the outer layer comprises the H2 receptor antagonist or salt thereof. According to the invention it is also possible for the outer layer to comprise the acid susceptible **proton pump inhibitor** or salt thereof and fort the inner layer to comprise the H2 receptor antagonist or salt thereof. According to a. . .

SUMM . . . is also disclosed a method for the manufacture of an oral tableted dosage form comprising amounts of an acid susceptible **proton pump inhibitor** or salt thereof and an H2 receptor antagonist or salt thereof pharmacologically effective in treating a condition related to dyspepsia, the method comprising forming a first layer comprising said acid susceptible **proton pump inhibitor** or salt thereof, an enteric coat surrounding said first layer, and a second layer comprising said H2 receptor antagonist or. . . coat. Also disclosed is a method for the manufacture of an oral dosage form comprising amounts of an acid susceptible **proton pump inhibitor** or salt thereof and an H2 receptor antagonist or salt thereof pharmacologically effective in treating a condition related to dyspepsia, the method comprising forming pellets comprising said acid susceptible **proton pump inhibitor** or salt thereof, covering said pellets with enteric coat, and mixing said pellets covered with said enteric coat with a. . .

SUMM . . . invention comprises filling a capsule capable of disintegrating in gastrointestinal fluids to release its contents with the mixture comprising enteric **proton pump inhibitor** pellets and a H2 receptor antagonist in powderous or granular form.

SUMM . . . method for the manufacture of the oral dosage form of the invention comprises forming a layer comprising an acid susceptible **proton pump inhibitor** or salt thereof and an H2 receptor antagonist or salt thereof, and covering said layer with an enteric coat.

SUMM . . . method for the manufacture of the oral dosage form of the invention comprises forming a mixture comprising an acid susceptible **proton pump inhibitor** or salt thereof and an H2 receptor antagonist or salt thereof, filling the mixture in a capsule capable of disintegrating. . .

SUMM . . . combined with the maintenance of inhibition as long as desired (by repeated administration of a composition comprising an acid susceptible **proton pump inhibitor**, preferably by repeated administration of the composition of the invention) can be expected to have a positive effect on the. . .

SUMM [0043] According to the invention the aforementioned mixture comprising an acid susceptible **proton pump inhibitor** or salt thereof and an H2 receptor antagonist or salt thereof can be used for the manufacture

of a medicament. . .

SUMM . . . or the concomitant administration of two separate oral dosage forms, one comprising a pharmacologically effective amount of an acid susceptible **proton pump inhibitor** or salt thereof, the other comprising a pharmacologically effective amount of an H2 receptor antagonist or salt thereof.

DRWD [0050] FIG. 1 a multiple unit tableted dosage form comprising an acid susceptible **proton pump inhibitor** in the form of enteric coating layered pellets in admixture with an H2-receptor antagonist dispersed in a pharmaceutical carrier;

DRWD . . . a tableted dosage form consisting of two halves, one of which comprises enteric coating layered pellets of an acid susceptible **proton pump inhibitor** in admixture with excipients whereas the other comprises an H2 receptor antagonist in admixture with excipients;

DRWD [0052] FIG. 3 a multiple-layered tableted dosage form comprising an acid susceptible **proton pump inhibitor** in a core surrounded by an enteric coating layer and a layer containing an H2 receptor antagonist dispersed in a. . .

DRWD [0053] FIG. 4 a tableted dosage form comprising an acid susceptible **proton pump inhibitor**, an H2-receptor antagonist and excipients in admixture, provided with an enteric coating;

DRWD [0054] FIG. 5 a capsule dosage form containing an acid susceptible **proton pump inhibitor** in enteric coating layered pellets in admixture with an H2 receptor antagonist and pharmaceutical excipients;

DRWD [0055] FIG. 6 an acid resistant capsule dosage form containing an acid susceptible **proton pump inhibitor**, an H2 receptor antagonist and excipients;

DETD . . . 3 and small pellets 2 distributed at random in the tablet body 2. The pellets 2 contain an acid susceptible **proton pump inhibitor** in form of the racemate, an alkaline salt or one of its enantiomers. The individually enteric coating layered units 2 (small beads, granules or pellets) containing the acid susceptible **proton pump inhibitor** and optionally containing alkaline substances, are mixed with the H2 receptor antagonist and conventional tablet excipients forming, in combination, the. . . dosage forms. By the expression "individual units" is meant small beads, granules or pellets, in the following referred to as **proton pump inhibitor** pellets. In compressing the mixture into tablets, care must be taken not to significantly affect the acid resistance of the enteric coated layered pellets. In regard of the core material for enteric coating layered pellets comprising an acid susceptible **proton pump inhibitor** reference is made to WO 97/25066, page 13, next but last paragraph, to page 15, end of second paragraph, which. . . next but last paragraph, to page 18, end of second paragraph, which are hereby incorporated by reference. The acid susceptible **proton pump inhibitor** pellets covered with enteric coating layer(s) may be further covered with one or more over-coating layers. In regard of such. . .

DETD [0059] Multi unit tablets. The enteric coated layered pellets comprising an acid susceptible **proton pump inhibitor** are mixed with the H2 receptor antagonist granules or with the prepared dry mixture comprising the H2 receptor antagonist. The. . .

DETD . . . total tablet weight. The preferred multiple unit table formulation thus consists of enteric coated layered pellets comprising the acid susceptible **proton pump inhibitor**, optionally in admixture with alkaline reacting compound(s), compressed into tablets with the prepared H2 receptor antagonist/excipient(s) mixture. The enteric coating. . . gastric fluid present in the proximal part of the small intestine where the dissolution and uptake of the acid susceptible **proton pump inhibitor** is desired. The enteric coating layered **proton pump inhibitor** pellets may also be covered with an overcoating layer before being formulated into tablets, and they may also contain one. . .

DETD . . . of the invention. After formulating the pellets by dry mixing (ordered mixture), spray coating or layering of the acid susceptible **proton pump inhibitor** onto seeds, or by extrusion/spheronization or granulation, the pellets are first optionally covered with the separating layer(s) and then with. . .

DETD . . . antagonist granules or dry powder, tablet excipients and other pharmaceutically acceptable additives and compressed into tablets. Alternatively, the enteric coated **proton pump inhibitor** pellets may be covered by a second layer containing the H2 receptor antagonist as described in the following examples. Furthermore,. . . with

film-forming agent(s) 6 to obtain a smooth surface. As a further alternative illustrated in FIG. 3 the acid susceptible **proton pump inhibitor** in form of a powder may be mixed with tablet excipients and compressed into a tablet 8 which is optionally. . .

DETD [0063] It is also possible to fill the acid susceptible **proton pump inhibitor** in form of enteric coated layered pellets in a sachet together with H2 receptor antagonist optionally mixed with excipients.

DETD [0064] FIG. 4 illustrated a tableted dosage form with a core 12 comprising an acid susceptible **proton pump inhibitor** and an H2 receptor antagonist dispersed in a pharmaceutical carrier, the core 12 being surrounded by an enteric coat 13.

DETD [0067] In general, the methods of WO 97/25066 for making oral pharmaceutical dosage forms comprising an acid susceptible **proton pump inhibitor** and an **antacid** agent or alginate can be adapted to suit the purpose of the invention by substituting part or the entire amount of **antacid** agent or alginate by a pharmacologically effective amount of an H2 receptor antagonist, the remainder of the **antacid** agent or alginate (if substitution is not 1:1 by weight) being omitted or substituted by excipients like microcrystalline cellulose, silica,. . .

DETD . . . symptoms. The dosage forms are administered once or several times a day. The typical daily dose of the acid susceptible **proton pump inhibitor** and the H2 receptor antagonist will depend on various factors such as individual requirements of patients, the mode of administration,. . . condition to be treated. In general each dosage form will comprise from 1 mg to 100 mg of acid susceptible **proton pump inhibitor** and from 1 to 800 mg of the H2 receptor antagonist. Preferably each dosage form will comprise from 5 to 50 mg of the acid susceptible **proton pump inhibitor** and from 5 to 200 mg of the H2 receptor antagonist. The multiple unit tablet preparation is also suitable for. . .

DETD [0072] By a slight modification this multiple unit tablet form can be made to comprise an **antacid** agent (instead of microcrystalline cellulose, 300 mg: microcrystalline cellulose, 100 g; calcium carbonate, 100 mg; magnesium oxide, 100 mg; all. . .

DETD [0073] Three-layered tableted dosage form. The tablet comprises the acid susceptible **proton pump inhibitor** omeprazole, a separating layer and a core layer comprising cimetidine hydrochloride. Batch size 1000 tablets.

First tablet layer
Cimetidine hydrochloride. . .

CLM What is claimed is:

1. An oral pharmaceutical dosage form comprising pharmacologically effective amounts of an acid susceptible **proton pump inhibitor** or a salt thereof and an H2 receptor antagonist or a salt thereof, and a pharmaceutically acceptable carrier.

2. The dosage form of claim 1, wherein the acid susceptible **proton pump inhibitor** is selected from lanzoprazole, omeprazole, pantoprazole, rabeprazole, pariprazole, leminoprazole, their pharmaceutically acceptable salts, enantiomers and salts of enantiomers.

. . . The dosage form of claim 1, comprising from 1 mg to 100 mg per single dose of an acid susceptible **proton pump inhibitor** or a salt thereof.

4. The dosage form of any of claims 1-3, wherein the acid susceptible **proton pump inhibitor** or a salt thereof is separated from the H2 receptor antagonist by an enteric coating.

11. The dosage form of any of claims 1-10, comprising from 100 mg to 1000 mg of **antacid** agent and/or alginate.

12. The dosage form of claim 11, wherein the **antacid** agent comprises one or several of aluminum hydroxide, calcium carbonate, magnesium carbonate, basic magnesium carbonate, magnesium hydroxide, magnesium oxide, sodium. . .

13. The dosage form of any of claims 1-12, wherein said acid susceptible **proton pump inhibitor** or a salt thereof is protected by an enteric coating layer and, optionally, a layer separating it from the enteric. . .

. . . claims 1-13, comprising two concentric layers optionally separated by one or more separating layer(s), one layer comprising said acid susceptible **proton pump inhibitor** or salt thereof, the other layer comprising said H2 receptor antagonist or salt thereof.

15. The dosage form of claim 14, wherein the inner layer comprises the acid susceptible **proton pump inhibitor** or salt thereof and the outer layer comprises the H2 receptor antagonist or salt thereof.

16. The dosage form of claims 14, wherein the outer layer comprises the acid susceptible **proton pump inhibitor** or salt thereof and the inner layer comprises the H2 receptor antagonist or salt thereof.

24. A method for the manufacture of an oral tableted dosage form comprising amounts of an acid susceptible **proton pump inhibitor** or salt thereof and an H2 receptor antagonist or salt thereof pharmacologically effective in treating a condition related to dyspepsia, the method comprising forming a first layer comprising said acid susceptible **proton pump inhibitor** or salt thereof, an enteric coat surrounding said first layer, and a second layer comprising said H2 receptor antagonist or. . .

25. A method for the manufacture of an oral dosage form comprising amounts of an acid susceptible **proton pump inhibitor** or salt thereof and an H2 receptor antagonist or salt thereof pharmacologically effective in treating a condition related to dyspepsia, the method comprising forming pellets comprising said acid susceptible **proton pump inhibitor** or salt thereof, covering said pellets with enteric coat, and mixing said pellets covered with said enteric coat with a. .

29. A method for the manufacture of an oral dosage form comprising amounts of an acid susceptible **proton pump inhibitor** or salt thereof and an H2 receptor antagonist or salt thereof pharmacologically effective in treating a condition related to dyspepsia, the method comprising forming a layer comprising an acid susceptible **proton pump inhibitor** or salt thereof and an H2 receptor antagonist or salt thereof, and covering said layer with an enteric coat.

30. A method for the manufacture of an oral dosage form comprising amounts of an acid susceptible **proton pump inhibitor** or salt thereof and an H2 receptor antagonist or salt thereof pharmacologically effective in treating a condition related to dyspepsia, the method comprising forming mixture comprising an acid susceptible **proton pump inhibitor** or salt thereof and an H2 receptor antagonist or salt thereof, filling said mixture in a capsule capable of disintegrating. .

31. The method of any of claims 24-30, wherein said acid susceptible **proton pump inhibitor** is selected from lansoprazole, omeprazole, pantoprazole, rabeprazole, pariprazole, leminoprazole, their pharmaceutically acceptable salts, enantiomers and salts of enantiomers.

. . . or the concomitant administration of two separate oral dosage forms, one comprising a pharmacologically effective amount of an acid susceptible **proton pump inhibitor** or salt thereof, the other comprising a pharmacologically effective amount of an H2 receptor antagonist or salt thereof.

L20 ANSWER 20 OF 31 USPATFULL on STN
Full Text
AN 2003:271551 USPATFULL
TI Novel substituted benzimidazole dosage forms and method of using same
IN Phillips, Jeffrey O., Ashland, MO, UNITED STATES
PI US 2003191159 A1 20031009
US 6699885 B2 20040302
AB . . . are methods, kits, combinations, and compositions for treating gastric acid disorders employing pharmaceutical compositions comprising a proton pump inhibiting agent (**PPI**) and a buffering agent in a pharmaceutically acceptable carrier.
SUMM . . . as critically ill patients, children, the elderly, and patients suffering from dysphagia. Therefore, it would be desirable to formulate a **proton pump inhibitor** solution or suspension which can be enterally delivered to a patient thereby providing the benefits of the **proton pump inhibitor** without the drawbacks of the current enteric-coated solid dosage forms.

SUMM [0013] Omeprazole, the first **proton pump inhibitor** introduced into use, has been formulated in many different embodiments such as in a mixture of polyethylene glycols, adeps solidus. . .

SUMM . . . the diseased or affected areas, namely the stomach and upper gastrointestinal tract, nor does this omeprazole formulation provide the immediate **antacid** effect of the present formulation.

SUMM . . . tablets or pellets, nor does it teach a convenient form which can be used to make an omeprazole or other **proton pump inhibitor** solution or suspension.

SUMM [0029] Fifth, excessive **antacid** intake (such as sodium bicarbonate) can result in drug interactions that produce serious adverse effects. For example, by altering gastric. . .

SUMM . . . a year while still maintaining 99% of its initial potency. It would be desirable to have an omeprazole or other **proton pump inhibitor** solution or suspension that could be stored at room temperature or in a refrigerator for periods of time which exceed. . .

SUMM [0033] It would, therefore, be desirable to have a **proton pump inhibitor** formulation, which provides a cost-effective means for the treatment of the aforementioned conditions without the adverse effect profile of H_2 receptor antagonists, antacids, and sucralfate. Further, it would be desirable to have a **proton pump inhibitor** formulation which is convenient to prepare and administer to patients unable to ingest solid dosage forms such as tablets or. . . the liquid formulation not clog indwelling tubes, such as nasogastric tubes or other similar tubes, and which acts as an **antacid** immediately upon delivery.

SUMM . . . another embodiment, oral dosage forms are disclosed comprising a combination of enteric-coated or delayed-released proton pump inhibiting agent with an **antacid**(s). Such forms may optionally comprise a non-enteric-coated proton pump inhibiting agent.

DETD [0065] For the purposes of this application, the term "**proton pump inhibitor**," or "**PPI**," or "proton pump inhibiting agent" means any agent possessing pharmacological activity as an inhibitor of H+, K+-ATPase. A class of. . . methods, kits, combinations, and compositions can include, for example, omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, pariprazole, or leminoprazole. The definition of "**PPI**," or "**proton pump inhibitor**," or "proton pump inhibiting agent" as used herein can also mean that the agent possessing pharmacological activity as an inhibitor. . .

DETD . . . to a pharmaceutical composition comprising a proton pump inhibiting agent, a buffering agent, and optionally a parietal cell activator. The **proton pump inhibitor** of the present invention may or may not be enteric coated, or sustained or delayed-release depending on the context in. . . present invention the proton pump inhibiting agent is not enteric coated, or sustained or delayed-release. In yet another embodiment the **proton pump inhibitor** is enteric coated, or sustained or delayed-release. And in another embodiment the composition may contain both an enteric coated proton. . .

DETD . . . with cysteine residues in the alpha subunit of the proton pump. Such active forms are included within the definition of "**PPI**," "**proton pump inhibitor**," or "proton pump inhibiting agent" herein.

DETD . . . pharmaceutical composition of the present invention is prepared by mixing omeprazole enteric-coated granules (Prilosec® AstraZeneca), or omeprazole base, or other **proton pump inhibitor** or derivatives thereof with a solution including at least one buffering agent (with or without a parietal cell activator, as discussed below). In one embodiment, omeprazole or other **proton pump inhibitor**, which can be obtained from powder, capsules, and tablets or obtained from the solution for iparenteral administration, is mixed with a sodium bicarbonate solution to achieve a desired final omeprazole (or other **proton pump inhibitor**) concentration. As an example, the concentration of omeprazole in the solution can range from approximately 0.4 mg/ml to approximately 10.0. . .

DETD [0110] The inventive solutions and other dosage forms of the present invention have pharmacokinetic advantages over standard enteric-coated and time-released **proton pump inhibitor** dosage forms, including: (a) more rapid drug absorbance time (about 10 to 60 minutes) following administration for the **proton pump inhibitor** solution or dry form versus about 1 to 3 hours following administration for the enteric-coated pellets; (b) the buffer solution protects the **proton pump inhibitor** from acid degradation prior to absorption; (c) the buffer acts as an **antacid** while the **proton pump inhibitor** is

being absorbed for rapid **antacid** relief; and (d) the solutions can be administered through an existing indwelling tube without clogging, for example, nasogastric or other. . .

DETD . . . agents such as methyl cellulose are desirable to use in order to reduce the settling of the omeprazole or other **proton pump inhibitor** or derivatives thereof from the suspension.

DETD [0115] The present invention further includes a pharmaceutical composition comprising omeprazole or other **proton pump inhibitor** and derivatives thereof and at least one buffering agent in a form convenient for storage, whereby when the composition is. . .

DETD . . . solution maintains greater than 90% of its potency for 12 months. By providing a pharmaceutical composition including omeprazole or other **proton pump inhibitor** with buffer in a solid form, which can be later dissolved or suspended in a prescribed amount of aqueous solution. . .

DETD . . . present pharmaceutical tablets or other solid dosage forms disintegrate rapidly in aqueous media and form an aqueous solution of the **proton pump inhibitor** and buffering agent with minimal shaking or agitation. Such tablets utilize commonly available materials and achieve these and other desirable objectives. The tablets or other solid dosage forms of this invention provide for precise dosing of a **proton pump inhibitor** that may be of low solubility in water. They may be particularly useful for medicating children and the elderly and. . .

DETD . . . after they are placed in water, and are readily dispersible to form a suspension containing a precise dosage of the **proton pump inhibitor**. The suspension tablets of this invention comprise, in combination, a therapeutic amount of a **proton pump inhibitor**, a buffering agent, and a disintegrant. More particularly, the suspension tablets comprise about 20 mg omeprazole and about 4-30 mEq. . .

DETD . . . magnesium silicate, magnesium aluminate, aluminum hydroxide or aluminum magnesium hydroxide. A particular alkali earth metal salt useful for making an **antacid** tablet is calcium carbonate.

DETD . . . chocolate, calcium and sodium bicarbonate and other alkaline substances, stimulate the parietal cells and enhance the pharmacologic activity of the **proton pump inhibitor** administered. For the purposes of this application, "parietal cell activator" or "activator" shall mean any compound or mixture of compounds. . .

DETD . . . amount of about 5 mg to 2.5 g per 20 mg dose of omeprazole (or equivalent pharmacologic dose of other **proton pump inhibitor**). The dose of activator administered to a mammal, particularly a human, in the context of the present invention should be sufficient to effect a therapeutic response (i.e., enhanced effect of **proton pump inhibitor**) over a reasonable time frame. The dose will be determined by the strength of the particular compositions employed and the. . .

DETD . . . The approximate effective ranges for various parietal cell activators per 20 mg dose of omeprazole (or equivalent dose of other **proton pump inhibitor**) are:

DETD . . . further alternative, sodium bicarbonate powder (about 975 mg per 20 mg dose of omeprazole (or an equipotent amount of other **proton pump inhibitor**) is compounded directly into the tablet. Such tablets are then dissolved in water or sodium bicarbonate 8.4%, or swallowed whole with an aqueous diluent.

B1. 10 mg Tablet Formula.

Omeprazole	10 (or lansoprazole or pantoprazole or other **proton pump inhibitor** in an equipotent amount)	mg
Calcium lactate	175	mg
Calcium glycerophosphate	175	mg
Sodium bicarbonate	250	mg
Aspartame calcium (phenylalanine)	0.5	mg
Colloidal silicon dioxide	12. . . starch	15 mg
Croscarmellose sodium	12	mg
Dextrose	10	mg
Peppermint	3	mg
Maltodextrin	3	mg
Mannitol	3	mg
Pregelatinized starch	3	mg

B2. 10 mg Tablet Formula.

Proton pump inhibitor: one of the following:		
Omeprazole	10	mg
Lansoprazole	15	mg
Pantoprazole sodium	20	mg
Rabeprazole sodium	10	mg
Other **proton pump inhibitor** in an equipotent amount		
Calcium lactate	375	mg
Calcium glycerophosphate	375	mg
Aspartame calcium (phenylalanine)	0.5	mg
Colloidal silicon dioxide	12	mg
Corn starch	15	mg
Croscarmellose sodium	12	mg
Dextrose	10	mg
Peppermint	3	mg
Maltodextrin	20	mg
Mannitol	30	mg
Pregelatinized starch	30	mg

B3. 10 mg Tablet Formula.

Proton pump inhibitor: one of the following:		
Omeprazole	10	mg
Lansoprazole	15	mg
Pantoprazole sodium	20	mg
Rabeprazole sodium	10	mg
Other **proton pump inhibitor** in an equipotent amount		
Sodium bicarbonate	750	mg
Aspartame sodium (phenylalanine)	0.5	mg
Colloidal silicon dioxide	12	mg
Corn starch	15	mg
Croscarmellose sodium	12	mg
Dextrose. . . mg		
Maltodextrin	20	mg
Mannitol	30	mg
Pregelatinized starch	30	mg

C1. 20 mg Tablet Formula.

Omeprazole	20	mg (or lansoprazole or pantoprazole or other **proton pump inhibitor** in an equipotent amount)
Calcium lactate	175	mg
Calcium glycerophosphate	175	mg
Sodium bicarbonate	250	mg
Aspartame calcium (phenylalanine)	0.5	mg
Colloidal silicon dioxide	12. . . sodium	12 mg
Dextrose	10	mg
Calcium hydroxide	10	mg
Peppermint	3	mg
Maltodextrin	3	mg
Mannitol	3	mg
Pregelatinized starch	3	mg

C2. 20 mg Tablet Formula.

Proton pump inhibitor: One of the following:		
Omeprazole	20	mg
Lansoprazole	30	mg
Pantoprazole	40	mg
Other **proton pump inhibitor** in an equipotent amount		
Calcium lactate	375	mg
Calcium glycerophosphate	375	mg
Aspartame calcium (phenylalanine)	0.5	mg
Colloidal silicon dioxide	12	mg
Corn starch	15	mg
Croscarmellose sodium	12	mg
Dextrose	10	mg
Peppermint	3	mg
Maltodextrin	20	mg
Mannitol	30	mg

Pregelatinized starch	30	mg

C3. 20 mg Tablet Formula.

Proton pump inhibitor: One of the following:		
Omeprazole	20	mg
Lansoprazole	30	mg
Pantoprazole	40	mg
Other **proton pump inhibitor** in an equipotent amount		
Sodium bicarbonate	750	mg
Aspartame sodium (phenylalanine)	0.5	mg
Colloidal silicon dioxide	12	mg
Corn starch	15	mg
Croscarmellose sodium	12	mg
Dextrose. . . mg		
Maltodextrin	20	mg
Mannitol	30	mg
Pregelatinized starch	30	mg

D1. Tablet for Rapid Dissolution.

Omeprazole	20	mg (or lansoprazole or pantoprazole or other **proton pump inhibitor** in an equipotent amount)
Calcium lactate	175	mg
Calcium glycerophosphate	175	mg
Sodium bicarbonate	500	mg
Calcium hydroxide	50	mg
Croscarmellose sodium	12	mg

D2. Tablet for Rapid Dissolution.

Proton pump inhibitor: One of the following:		
Omeprazole	20	mg
Lansoprazole	30	mg
Pantoprazole	40	mg
Rabeprazole sodium	20	mg
Esomeprazole magnesium	20	mg
Other **proton pump inhibitor** in an equipotent amount		
Calcium lactate	300	mg
Calcium glycerophosphate	300	mg
Calcium hydroxide	50	mg
Croscarmellose sodium	12	mg

D3. Tablet for Rapid Dissolution.

Proton pump inhibitor: One of the following:		
Omeprazole	20	mg
Lansoprazole	30	mg
Pantoprazole	40	mg
Rabeprazole sodium	20	mg
Esomeprazole magnesium	20	mg
Other **proton pump inhibitor** in an equipotent amount		
Sodium bicarbonate	700	mg
Trisodium phosphate dodecahydrate	100	mg
Croscarmellose sodium	12	mg

E1. Powder for Reconstitution for Oral Use (or per ng tube).

Omeprazole	20	mg (or lansoprazole or pantoprazole or other **proton pump inhibitor** in an equipotent amount)
Calcium lactate	175	mg
Calcium glycerophosphate	175	mg
Sodium bicarbonate	500	mg
Calcium hydroxide	50	mg
Glycerine	200	mg

E2. Powder for Reconstitution for Oral Use (or per ng tube).

Proton pump inhibitor: One of the following:		
Omeprazole	20	mg
Lansoprazole	30	mg
Pantoprazole	40	mg

Rabeprazole sodium	20	mg
Esomeprazole magnesium	20	mg
Other **proton pump inhibitor** in an equipotent amount		
Calcium lactate	300	mg
Calcium glycerophosphate	300	mg
Calcium hydroxide	50	mg
Glycerine	200	mg
E3. Powder for Reconstitution for Oral Use (or per ng tube).		
Proton pump inhibitor: One of the following:		
Omeprazole	20	mg
Lansoprazole	30	mg
Pantoprazole	40	mg
Rabeprazole sodium	20	mg
Esomeprazole magnesium	20	mg
Other **proton pump inhibitor** in an equipotent amount		
Sodium bicarbonate	850	mg
Trisodium phosphate	50	mg
F1. 10 mg Tablet Formula.		
Omeprazole	10	mg (or lansoprazole or pantoprazole or other **proton pump inhibitor** in an equipotent amount)
Calcium lactate	175	mg
Calcium glycerophosphate	175	mg
Sodium bicarbonate	250	mg
Polyethylene glycol	20	mg
Croscarmellose sodium	12	mg
Peppermint	3	mg
Magnesium silicate	1	mg
Magnesium stearate	1	mg
F2. 10 mg Tablet Formula.		
Proton pump inhibitor: One of the following:		
Omeprazole	10	mg
Lansoprazole	15	mg
Pantoprazole sodium	20	mg
Rabeprazole sodium	10	mg
Esomeprazole magnesium	10	mg
Other **proton pump inhibitor** in an equipotent amount		
Calcium lactate	475	mg
Calcium glycerophosphate	250	mg
Polyethylene glycol	20	mg
Croscarmellose sodium	12	mg
Peppermint	3	mg
Magnesium silicate	10	mg
Magnesium stearate	10	mg
F3. 10 mg Tablet Formula.		
Proton pump inhibitor: One of the following:		
Omeprazole	10	mg
Lansoprazole	15	mg
Pantoprazole sodium	20	mg
Rabeprazole sodium	10	mg
Esomeprazole magnesium	10	mg
Other **proton pump inhibitor** in an equipotent amount		
Sodium bicarbonate	700	mg
Polyethylene glycol	20	mg
Croscarmellose sodium	12	mg
Peppermint	3	mg
Magnesium silicate	10	mg
Magnesium stearate	10	mg
G1. 10 mg Tablet Formula.		
Omeprazole	10	mg (or lansoprazole or pantoprazole or other **proton pump inhibitor** in an equipotent amount)
Calcium lactate	200	mg

Calcium glycerophosphate	200	mg
Sodium bicarbonate	400	mg
Croscarmellose sodium	12	mg
Pregelatinized starch	3	mg

G2. 10 mg Tablet Formula.

Proton pump inhibitor: One of the following:		
Omeprazole	10	mg
Lansoprazole	15	mg
Pantoprazole sodium	20	mg
Rabeprazole sodium	10	mg
Esomeprazole magnesium	10	mg
Other **proton pump inhibitor** in an equipotent amount		
Calcium lactate	400	mg
Calcium glycerophosphate	400	mg
Croscarmellose sodium	12	mg
Pregelatinized starch	3	mg

G3. 10 mg Tablet Formula.

Proton pump inhibitor: One of the following:		
Omeprazole	10	mg
Lansoprazole	15	mg
Pantoprazole sodium	20	mg
Rabeprazole sodium	10	mg
Esomeprazole magnesium	10	mg
Other **proton pump inhibitor** in an equipotent amount		
Sodium bicarboante	750	mg
Croscarmellose sodium	12	mg
Pregelatinized starch	3	mg

All of the tablets and powders of this Example. . .

DETD [0169] Standard Tablet of **Proton Pump Inhibitor** and Buffering Agent.

DETD [0173] **Proton Pump Inhibitor** Central Core Tablet.

DETD . . . activate the effervescent agents and create the desired solution. In addition, lansoprazole 30 mg (or an equipotent dose of other **proton pump inhibitor**) can be substituted for omeprazole.

DETD . . . patients, 9 were excluded from the study, all based upon insufficient data about commencement, duration or outcome in treatment with **proton pump inhibitor** therapy. This left 24 patients with enough data to draw conclusions.

DETD [0188] Of the 24 remaining patients, 18 were males and 6 females. Ages at implementation of **proton pump inhibitor** therapy ranged from 2 weeks of age to 9 years old. Median age at start of therapy was 26.5 months. . . . in a few patients. Six patients had neither pH nor endoscopic documentation of gastroesophageal reflux disease, but were tried on **proton pump inhibitor** therapy based on symptomatology alone.

DETD [0192] The **proton pump inhibitor** suspension used in this group of patients was Choco-Base suspension of either lansoprazole or omeprazole. The dosing was very uniform,. . .

DETD [0193] Most patients responded favorably to and tolerated the once daily dosing of Choco-Base **proton pump inhibitor** suspension. Two patients had documented adverse effects associated with the use of the **proton pump inhibitor** suspension. In one patient, the mother reported increased burping up and dyspepsia, which was thought to be related to treatment. . .

DETD . . . and (4) inconclusive. Of 24 patients with sufficient data for follow up, 18 showed improvement in symptomatology upon commencement of **proton pump inhibitor** therapy [72%]. The seven who did not respond were analyzed and grouped. Three showed no change in symptomatology and clinical. . . 8). Setting aside the cases in which therapy was stopped before conclusions could be drawn and the case in which **proton pump inhibitor** therapy was for purely prophylactic reasons, leaves (17/21) 81% of patients that responded to Choco-Base suspension. This means that 19% (4/21) of patients received no apparent benefit from **proton pump inhibitor** therapy. Of all these patients, only 4% complained of worsening symptoms and the side effects were 4% (1/21) and were. . .

DETD . . . a pro-kinetic agent and H-2 blocker therapy. Nonetheless, many patients fail this treatment protocol and become surgical candidates. In adults, **proton pump inhibitor** therapy is effective in 90% of those

treated for gastroesophageal reflux disease. As a medical alternative to the H-2 blockers,. . . appropriate dosage should be in this group of patients. A recent review by Israel D., et al. suggests that effective **proton pump inhibitor** dosages should be higher than that originally reported, i.e., from 0.7 mg/kg to 2 or 3 mg/kg omeprazole. Since toxicity. . .

DETD [0198] In the ICU setting, the University of Missouri-Columbia has been using an unflavored **proton pump inhibitor** suspension given once daily per various tubes (nasogastric, g-tube, jejunal feeding tube, duo tube, etc.) for stress ulcer prophylaxis. It. . .

DETD . . . in the adult population, but this can be attributed to the refractory nature of their illness, most having failed prior non-**proton pump inhibitor** treatment. The population in this study is not indicative of general practice populations.

DETD [0202] **Proton pump inhibitor** therapy is a beneficial therapeutic option in the treatment of reflux related symptoms in the pediatric population. Its once daily. . .

DETD [0208] In all four of the above formulations, lansoprazole or other **proton pump inhibitor** can be substituted for omeprazole in equipotent amounts. For example, 300 mg of lansoprazole may be substituted for the 200. . .

DETD . . . proton pump and effectively block activated proton pumps (primarily those inserted into the secretory canalicular membrane). By further administering the **proton pump inhibitor** with one of these activators or enhancers, there is a synchronization of activation of the proton pump with the absorption and subsequent parietal cell concentrations of the **proton pump inhibitor**. As illustrated in FIG. 4, this combination produced a much longer pharmacologic effect than when the **proton pump inhibitor** was administered alone.

DETD [0213] Combination Tablet Delivering Bolus And Time-Released Doses of **Proton Pump Inhibitor**

DETD [0279] 1. Currently taking $H_{2\text{-receptor}}$ antagonist, **antacid**, or sucralfate.

DETD [0280] 2. Recent (within 7 days) therapy with lansoprazole, omeprazole, or other **proton pump inhibitor**.

DETD [0293] Intraveneous **Proton Pump Inhibitor** in Combination With Oral Parietal Cell Activator

DETD . . . can be administered either within about 5 minutes before, during or within about 5 minutes after the IV dose of **proton pump inhibitor**.

DETD [0299] Applicant expects that these studies will demonstrate that significantly less IV **proton pump inhibitor** is required to achieve therapeutic effect when it is given in combination with an oral parietal cell activator.

DETD [0300] Additionally, administration kits of IV **proton pump inhibitor** and oral parietal cell activator can be packaged in many various forms for ease of administration and to optimize packing. . .

DETD . . . receiving ketoconazole or itraconazole or enteral tube feedings; or had received an investigational drug within 30 days, omeprazole or another **proton pump inhibitor** within 5 days, or warfarin or nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, within 24 h. Administration of the study drug. . .

DETD [0332] A Comparison of the Pharmacokinetics and Pharmacodynamics of Omeprazole Delivered Orally with Different Doses of **Antacid** in Fasted Subjects

DETD [0335] Period 1: 1 **antacid** tablet (30 mEq of 1 part sodium bicarbonate to 3 parts calcium carbonate) plus 40 mg omeprazole powder was administered. . .

DETD [0338] Period 5: 1 **antacid** tablet (30 mEq of 1 part sodium bicarbonate to 1 part calcium carbonate) plus 40 mg omeprazole powder was administered. . .

DETD . . . the drug product by site staff directly onto the dorsal mid-tongue. Immediately thereafter, subjects were administered one or two chewable **antacid** tablets and began chewing. Each subject continued to chew the tablet(s), while mixing it with the omeprazole powder, carefully avoiding. . .

DETD [0384] The chewable **antacid** tablets were produced by Murty Pharmaceuticals, Inc. (518 Codell Drive, Lexington, Ky. 40509-1016) and contained sodium bicarbonate and calcium carbonate,. . .

DETD [0388] VI. **Proton pump inhibitor** Compositions and Method for Optimizing the Buffer to be Administered in Combination With a **Proton Pump Inhibitor**

DETD . . . proton pump inhibiting agents, for example, can be formulated or coadministered with one or more buffers sufficient to protect the **proton pump inhibitor** in any environment, with the ultimate goal being to deliver a **proton pump inhibitor** to the stomach (or other environment) either via a liquid, a powder or solid dosage form that produces an immediate release of active drug to the site of delivery such that the **proton pump inhibitor** is quickly available for absorption. Accordingly, Applicant has found that certain amounts of buffers coadministered or mixed with certain proton pump inhibiting agents prevent acid degradation of the **proton pump inhibitor** when the buffers produce a pH in the stomach or other site of environment that is equal to the pKa of the **proton pump inhibitor** plus an amount sufficient to protect the **proton pump inhibitor** from acids and provide undegraded and bioactive **proton pump inhibitor** to the blood upon administration (e.g., a final pH of pKa of **proton pump inhibitor**+0.7 log value will reduce the degradation to about 10%). Such buffers should interact with hydrogen ion at rates that exceed the interaction of hydrogen ion with the **proton pump inhibitor**. Thus, the solubilities of the buffers and proton pump inhibiting agents are important considerations because solubility is a key determinant. . .

DETD [0391] Typically, a **proton pump inhibitor** formulation of the present invention comprises two primary components: a **proton pump inhibitor** and an Essential Buffer. An Essential Buffer may include a buffer or combination of buffers that interact with HCl (or other acids in the environment of interest) faster than the **proton pump inhibitor** interacts with the same acids. When placed in a liquid phase (usually in water), the Essential Buffer produces and maintains a pH of at least the pKa of the **proton pump inhibitor**. In one embodiment, by raising the pH of the environment to the same of the pKa of the **proton pump inhibitor** plus about 0.7 log value (or greater), the expected degradation (ionization) can be reduced from about 50% to about 10%.. . . pH" is the lowest pH of the environment of interest needed to minimize or eliminate the acid-induced degradation of the **proton pump inhibitor**. The buffering agent(s) employed may raise the pH of the environment to the Essential pH such that 30%, 40% or 50% of the **proton pump inhibitor** is undegraded, or be present in an amount sufficient to substantially protect (i.e., greater than 50% stability) the **proton pump inhibitor**.

DETD [0392] In another embodiment, the Essential pH is the pKa of the **proton pump inhibitor**. In a further embodiment, the Essential pH is the sum of the pKa of the **proton pump inhibitor** plus log 0.7. A log value of about 0.7 is added to the pKa, which represents a decrease of about 5.01187% in stability of the **proton pump inhibitor** from the pKa plus 1 log value, thus resulting in a stability of approximately 90%, a value widely accepted as. . .

DETD . . . (Essential Buffer Capacity ("EBC")) to maintain the elevated pH of the environment (usually gastric) throughout the dwell time that the **proton pump inhibitor** is passed from the environment and into the blood.

DETD . . . the value that leads to tissue irritation or damage and above a lower limit for the Essential pH of the **proton pump inhibitor**. Secondary Essential Buffers are not required in every formulation but can be combined with Primary Essential Buffers to produce a. . .

DETD . . . dose of buffer to protect acid labile substituted benzimidazole proton pump inhibiting agents (and other drugs) is useful for efficacious **proton pump inhibitor** delivery to and action upon parietal cell proton pumps, particularly when the **proton pump inhibitor** is administered as an immediate release product designed to disintegrate in the stomach rather than a traditional delayed-release product designed. . . the buffer(s) to be used, as well as calculations to determine Essential pH, buffering capacity, and volume measurements for individual **proton pump inhibitor** doses based on their respective solubilities and pKa's. Such inventive methods are applicable for determining the type and amount of buffer(s) necessary to protect the **proton pump inhibitor** in an array of environments (e.g., mouth, esophagus, stomach, duodenum, jejunum, rectal vault, nasogastric tube, or a powder, tablet, capsule,. . .

DETD [0398] The Essential Buffering Capacity ("EBC") is the capacity of a **proton pump inhibitor**/buffer formulation to resist degradation from its environment. The buffering capacity of a **proton pump inhibitor**/buffer formulation is primarily derived from components of the formulation that possess the ability to combine with acids (H+ ions) from the environment. The EBC contributes to both acid neutralization

(**antacid** effect) and to maintaining an environmental pH>pKa+0.7 to protect proton pump inhibiting agents from acid degradation throughout the dwell time.. . . (or other environment) at a somewhat constant level within a desired range for a period of time so that the **proton pump inhibitor** can be absorbed from the gastric or other environment. Accordingly, the Essential Buffer is generally more rapid in its complexation with HCl (or other acid) than the **proton pump inhibitor** administered so that the Essential Buffer is capable of protecting the **proton pump inhibitor**.

DETD [0401] Secondary Essential Buffers do not play an important role in protecting the **proton pump inhibitor** from early acid-induced degradation. Because they do not work as rapidly, they do not play a major role in **proton pump inhibitor** protection through the dwell time. Other buffers ("Non-Essential Buffers") can be added to the Primary and/or Secondary Essential Buffers to provide a latent **antacid** effect that extends beyond the **antacid** effect of Essential Buffers.

DETD . . . feeds or other sources. In general, the higher the pH of the gastric environment, the greater the stability of the **proton pump inhibitor**, and thus the more time it has to undergo absorption into the blood and reach and act upon the proton. . .

DETD . . . pH" is the lowest pH of the environment of interest needed to minimize or eliminate the acid-induced degradation of the **proton pump inhibitor** during the dwell time in the environment. It is generally expressed herein as pH range. Such pH is the pH of the environment in which the **proton pump inhibitor**/buffer formulation resides. For example, the environment may be a storage container or the stomach. The environment presents a set of conditions to the **proton pump inhibitor**/buffer, such as temperature, pH, and the presence or absence of water. The dwell time is the time that the **proton pump inhibitor** dwells in a specific environment, i.e., the GI tract prior to its passage into a different environment, i.e. the blood. . . container of dry, powdered formulation. As used herein, "Resultant pH" is the pH that is the result of adding a **proton pump inhibitor**/buffer formulation to an environment of interest. "Formulation pH" is the pH of the **proton pump inhibitor**/buffer formulation when it is in liquid form.

DETD [0411] A **proton pump inhibitor** dose within its calculated pH_E range is designed to ensure sufficient **proton pump inhibitor** protection from acid degradation such that delivery to and action upon proton pumps occur. In one desirable embodiment, the pH_E is the sum of the pKa of a given **proton pump inhibitor** plus about 0.7. The pKa is defined as the pH at which 50% of a chemical is in the ionized form. When the pH of the environment equals the pKa of the **proton pump inhibitor**, then 50% ionization (degradation) of the **proton pump inhibitor** occurs. However, by adding the factor of 0.7, this ionization is reduced to 90%.

DETD . . . is the range of pH elevation in which the lower limit is the sum of the pKa of a given **proton pump inhibitor**+0.7 log, and the upper limit is the pH at which elimination of acid degradation occurs without producing tissue irritation from. . .

DETD . . . buffer is an important aspect of the tissue destructive potential of an alkaline substance. Therefore, the SRF for any given **proton pump inhibitor** begins at the sum of the pKa of the **proton pump inhibitor**+0.7, and extends upwards to a pH of about 10.9.

DETD [0417] pH_E of **proton pump inhibitor**=pKa of **proton pump inhibitor**+0.7.

DETD . . . a factor of 10, any local effects within the stomach that may produce areas of lower pH that might cause **proton pump inhibitor** degradation. A value of +1 log value is also supported by the observation that weak bases operate most efficiently at. . .

DETD . . . However, magnesium hydroxide is not rapid in onset and care should be taken to ensure that early degradation of the **proton pump inhibitor** does not occur. Early degradation can be avoided by making a tablet comprising **two layers**: an inner layer of **proton pump inhibitor** and sodium bicarbonate, and an outer layer of magnesium hydroxide dried gel or magnesium oxide with suitable disintegrant such that. . . rapidly disintegrate in the stomach. Alternatively, the inner layer can contain the magnesium buffer and the outer layer has the **proton pump inhibitor** and sodium bicarbonate.

DETD . . . best suited in an outer layer of a tablet formulation with the inner layer comprising a rapid acting buffer with **proton pump inhibitor** (or vice versa). Alternatively, mixtures of the buffers can

be employed for the outer layer. If developing a liquid formulation. . .

DETD [0430] As mentioned above, the pKa of a given **proton pump inhibitor** indicates inherent stability with respect to acid degradation; the lower the pKa, the more stable the **proton pump inhibitor**. The solubility of the **proton pump inhibitor** will also dictate the rate at which the **proton pump inhibitor** complexes with, and is degraded by, acid. These two physicochemical characteristics (pKa and solubility) of the **proton pump inhibitor** interact with the physicochemical characteristics of the buffer(s) (pH, buffering capacity and rate of buffering action) in the presence of acid in the environment to determine the degradation of the **proton pump inhibitor** over time. The less soluble a **proton pump inhibitor** is in water, the lower the initial degradation when placed in an acidic environment. The following Table 11 elaborates on. . .

DETD . . . overall pH of the gastric contents should be kept at least at the pKa+0.7 (i.e., 3.7) from the time the **proton pump inhibitor** in solution comes into contact with the gastric acid continuing throughout the dwell time. Essential Buffers for liquid formulations of. . .

DETD [0433] Another option for rabeprazole sodium (as well as any sodium salt of a **proton pump inhibitor**, which would tend to be more soluble than the base form) is to reduce the solubility of rabeprazole sodium when. . .

DETD . . . that possess high pKa's, such as rabeprazole sodium, a two-part liquid formulation can be utilized. The liquid part has the **proton pump inhibitor** and a high pH, but a low mEq buffering capacity. The liquid part is added to a second part that. . .

DETD . . . as a tablet, capsule or powder with a buffer(s), which disintegrate and reach solution at a rate that exceeds the **proton pump inhibitor** and thereby provides the Essential pH for protection of the **proton pump inhibitor** prior to its dissolution and interaction with the acid in the environment. Further, the tablet or capsule may be formulated to possess an outer portion of buffer and an inner portion comprising **proton pump inhibitor**, or a blend of **proton pump inhibitor** and buffer. Additional methods include formulating the buffer in a smaller particle size (e.g., micronized) and the **proton pump inhibitor** in a larger particle size. This results in the disintegration of the buffer component prior to disintegration of the **proton pump inhibitor** component. All of these methods of formulation aim to create an environment of stability for the **proton pump inhibitor** during the dwell time.

DETD . . . a buffer that raises the pH of the environment to greater than or equal to the pH_E of a particular **proton pump inhibitor** in a time sufficient to prevent significant degradation of the **proton pump inhibitor**. In one embodiment, the rapid acting buffer raises the pH to at least the pKa of the **proton pump inhibitor** plus 0.7 log value within 10 minutes.

DETD . . . the onset of pH change to equal to or greater than the pH_E+0.7 begins before the acid-induced degradation of the **proton pump inhibitor** occurs, and (2) the Resultant pH at or greater than the pH_E+0.7 lasts throughout the dwell time, which is typically. . . the particle size of the buffer(s) can be reduced to enhance the dissolution rate while the particle size of the **proton pump inhibitor** can be increased. Disintegrants can be added to enhance the availability of poorly soluble buffers.

DETD . . . pH of the gastric contents (or other environment) should be kept at greater than about 4.8 from the time the **proton pump inhibitor** in solution comes into contact with the gastric acid continuing throughout the dwell time.

DETD . . . that contain a tablet in a tablet, the Essential Buffer complexes with the acid at a faster rate than the **proton pump inhibitor** it is intended to protect.

DETD [0452] When the **proton pump inhibitor**/buffer formulation is placed in the environment, the **proton pump inhibitor** is subject to degradation by the acid in that environment. As depicted in FIG. 9, **proton pump inhibitor** solubility, the pKa of the **proton pump inhibitor**, and the amount and concentration of acid (H+ ion) encountered in the environment are variables that can be used to determine the appropriate candidate as an Essential Buffer. Early degradation occurs when the soluble portion of the **proton pump inhibitor** (that portion available for immediate interaction with H+ ion) undergoes hydrolysis by H+ ion. proton pump inhibiting agents

differ in their solubility and, therefore, those that are more soluble have a potential for a higher portion of **proton pump inhibitor** degraded by early interaction with H+ ion. The pKa of the **proton pump inhibitor** and the pH of the environment of the stomach (or other site of interest) after addition of the **proton pump inhibitor**/buffer formulation (Resultant pH) can be used to determine the desirable Essential Buffer. By measuring the Resultant pH over time, the. . .

DETD . . . has been described in part for use in evaluating antacids by Beneyto J E, et. al., Evaluation of a New **Antacid**, Almagate, ARZNEIM-FORSCH/DRUG RES 1984; 34 (10 A):1350-4; Kerkhof NJ, et al, pH-Stat Tiration of Aluminum Hydroxide Gel, J. PHARM. SCI.. . .

DETD . . . products. In addition, a sample of the test solution can be taken during the experiment to evaluate the extent of **proton pump inhibitor** degradation at various times. Those buffers with a suitable profile as exemplified in FIG. 9 able to maintain pH greater. . .

DETD . . . alkaline buffer, included in the dose and calculated to maintain the Essential pH range and thereby protect any substituted benzimidazole **proton pump inhibitor** in the gastric (or other) environment. In patients requiring continuing **proton pump inhibitor** administration (e.g. daily), more buffering capacity may be necessary with the first dose or first few doses than with subsequent doses because the **proton pump inhibitor** may encounter more acid with the initial doses. Subsequent doses will require less buffering capacity because the initial **proton pump inhibitor** doses will have reduced gastric acid production. The EBC could therefore be reduced in subsequent doses. The product's buffering capacity. . .

DETD [0459] Numerous references are available to assist the skilled artisan in identifying a suitable buffer companion with a **proton pump inhibitor** to determine the desirable characteristics stated herein. See, e.g., Holbert, et. al., A Study of **Antacid** Buffers: I. The Time Factor in Neutralization of Gastric Acidity, J. AMER. PHARM. ASSN. 36: 149-51 (1947); Lin, et. al.,. . .

DETD [0461] The Desirable Volume ("DV") of a **proton pump inhibitor** dose may affect **proton pump inhibitor** delivery to and action upon parietal cell proton pumps. The DV of a dose is partly based on the EBC. For liquid formulations, a desirable volume should deliver sufficient buffer to act as an **antacid** to neutralize a substantial amount of gastric or other acids. For solid formulations such as tablets, a nominal amount of. . .

DETD . . . butterscotch, and peanut butter flavorings, used alone or in any combination. Similarly, all substances included in the formulation of any **proton pump inhibitor** product, including but not limited to, activators, antifoaming agents, potentiators, antioxidants, antimicrobial agents, chelators, sweeteners, thickeners, preservatives, or other additives. . .

DETD [0472] The pH_E, the EBC, and the DV of a **proton pump inhibitor** dose may affect **proton pump inhibitor** delivery to, and action upon, parietal cell proton pumps. The following calculations tailor an Essential Buffer dose for any substituted benzimidazole **proton pump inhibitor** to promote **proton pump inhibitor** efficacy in an oral administration.

DETD . . . order to enhance the shelf-life, higher pH values would be anticipated within the range of acceptable pH_E for a given **proton pump inhibitor**. As an example, rabeprazole suspensions containing various buffers were evaluated for color change because degradation of proton pump inhibiting agents. . .

DETD [0518] Similar calculations may be performed for any substituted benzimidazole **proton pump inhibitor** and appropriate buffer(s) including, but not limited to, those exemplified above. One skilled in the art will appreciate that the. . . above steps is not critical to the invention. The above calculations may be used for formulations comprising one or more **proton pump inhibitor** and one or more buffers.

DETD . . . mEq.

Formulation 5: Veterinary Formulation of Omeprazole
This formulation is particularly well suited for animals rather than humans because the dose of **proton pump inhibitor** is high. EBC = 75 mEq Essential pH (omeprazole pKa = 3.9 + 0.7 ≥ 4.6)

Proton pump inhibitor:
Omeprazole powder 500 mg (a range of 350 to 700 mg)
Primary Essential Buffer(s):
Sodium bicarbonate 5 g (59.5. . . Any Secondary Essential Buffer(s) may be added in higher or lower amounts to adjust pH for desired stability and additive **antacid** or buffering effect.)
DETD . . . the time of use.

Formulation 6: Veterinary Formulation of Lansoprazole
Essential pH (lansoprazole pKa=4.1 + 0.7 ≥ 4.8)
EBC = 71.4 mEq

Proton pump inhibitor:
Lansoprazole powder 750 mg
Primary Essential Buffer(s):
Sodium bicarbonate 6 g (71.4 mEq)

(* Any Secondary Essential Buffer(s) may be added in higher or lower amounts to adjust pH for desired stability and additive **antacid** or buffering effect.)
DETD . . . of use.

Formulation 7: Veterinary Formulation of Lansoprazole
Essential pH (lansoprazole pKa = 4.1 + 0.7 ≥ 4.8)
EBC = 63.3 mEq

Proton pump inhibitor:
Lansoprazole powder 750 mg
Primary Essential Buffer(s)
Sodium bicarbonate 5 g (59.5 mEq)
Secondary Essential Buffer(s):
Sodium carbonate 400 mg* (3.8 mEq)

(* Any Secondary Essential Buffer(s) may be added to adjust pH for desired stability and additive **antacid** or buffering effect.)
DETD . . . use.

Formulation 8: Veterinary Formulation of Esomeprazole Magnesium
Essential pH (esomeprazole pKa = 3.9 + 0.7 ≥ 4.6)
EBC = 53.2 mEq

Proton pump inhibitor:
Esomeprazole magnesium powder 500 mg
Primary Essential Buffer(s):
Sodium bicarbonate 5 g (47.6 mEq)
Dibasic sodium phosphate 800 mg. . . Any Secondary Essential Buffer(s) may be added in higher or lower amounts to adjust pH for desired stability and additive **antacid** or buffering capacity.)
DETD . . . mEq)

(*Any Secondary Essential Buffer(s) may be added in higher or lower amounts to adjust pH for desired stability and additive **antacid** or buffering capacity.)
DETD . . . may be added to achieve esomeprazole concentrations ranging from 0.2 to 20 mg/mL.

Formulation 10: Veterinary Formulation: Buffer Base Without **Proton Pump Inhibitor**
EBC = 71.4 mEq

Primary Essential Buffer:

Sodium bicarbonate 6 g 71.4 mEq
Optional Secondary Essential Buffer:
Tribasic sodium phosphate. . . mg*

(*Any Secondary Essential Buffer may be added in higher or lower amounts to adjust pH for desired stability and additive **antacid** or buffering capacity.)

DETD . . . butterscotch flavor 100 mg, thaumatin powder 5 mg, and sucrose 30 Gm. Q.s. to 100 mL with distilled water. A **proton pump inhibitor** or other acid-labile drug may be added by the compounding pharmacist selected from available proton pump inhibiting agents or acid-labile drugs from powder or enteric-coated oral solid dosage forms. Different volumes of water may be added to achieve **proton pump inhibitor** concentrations ranging from 0.8 to 20 mg/mL. If other acid labile drugs are employed, the range of concentrations would be. . .

DETD . . . Essential Buffer may range from about 4 mEq to about 30 mEq per dose.

Formulation 11: Oral Buffer Complex Without **Proton Pump Inhibitor** (for general use to protect acid labile drugs) Multidose Composition

Primary Essential Buffer:
Dibasic sodium phosphate or sodium- 10 g (range 2. . . mg

(*Any Secondary Essential Buffer may be added in higher or lower amounts to adjust pH for desired stability and additive **antacid** or buffering capacity.)

DETD . . . maple, butter pecan and other flavorings as have been outlined previously. Different volumes of water may be added to achieve **proton pump inhibitor** concentrations ranging from 0.8 to 20 mg/mL.

DETD [0536] Weigh out approximately 60 g of the formulation. Add **proton pump inhibitor** (or other acid-labile drug) typically in the amount equivalent to 10 doses (range 1 dose to 30 doses).

DETD [0537] Q.s. to 100 mL with distilled water.

Formulation 12: Oral Buffer Complex Without **Proton Pump Inhibitor** For General Use to Protect Acid Labile Drugs; Protein Free, Multi-Dose Example

Primary Essential Buffer:
Sodium bicarbonate 5 g (range 2 g. . .
(*Any Secondary Essential Buffer may be added in higher or lower amounts to adjust pH for desired stability and additive **antacid** or buffering capacity.)

DETD . . . protected from light and moisture, such as in a foil packet. Weigh out approximately 60 g of the formulation. Add **proton pump inhibitor** (or other acid-labile drug) typically in the amount equivalent to 10 doses (range=1 dose to 30 doses).

DETD [0539] Q.s. to 100 mL with distilled water. Different volumes of water may be added to achieve **proton pump inhibitor** concentrations ranging from 0.8 to 20 mg/mL.

Formulation 13: Buffer Complex Without **Proton Pump Inhibitor** For General Use to Protect Acid Labile Drugs; Protein Free, Lactose Free Multidose Example

Proton pump inhibitor:
None (to be added later, e.g. by compounding pharmacist)
Primary Essential Buffer(s):
Sodium bicarbonate 8 g (range 2 g. . .

DETD [0543] Weigh out approximately 60 g of the formulation. Add **proton pump inhibitor** (or other acid-labile drug) typically in the amount equivalent to 10 doses (range=1 dose to 30 doses). Q.s. to 100 mL with distilled water. Different volumes of water may be added to achieve **proton pump inhibitor** concentrations ranging from 0.3 to 20 mg/mL.

Formulation 14: Buffer Complex Without **Proton Pump Inhibitor** For General Use to Protect Acid Labile Drugs; Protein Free, Multi-Dose Example

Proton pump inhibitor:
None (to be added later, e.g. by compounding pharmacist)
Primary Essential Buffer(s):
Dibasic sodium phosphate 8 g (range 2. . .

DETD [0545] Weigh out approximately 60 g of the formulation. Add **proton pump inhibitor** (or other acid-labile drug) typically in the amount equivalent to 10 doses (range=1 dose to 30 doses). Q.s. to 100 mL with distilled water. Different volumes of water may be added to achieve **proton pump inhibitor** concentrations ranging from 0.8 to 20 mg/mL.

Formulation 15: Buffer Complex Without **Proton Pump Inhibitor** For General Use to Protect Acid Labile Drugs; Protein Free, Multi-Dose Example

Proton pump inhibitor:
None (to be added later, e.g. by compounding pharmacist)
Primary Essential Buffer(s):
Sodium bicarbonate 8 g (range 1 g. . .

DETD . . . protected from light and moisture, such as in a foil packet. Weigh out approximately 60 g of the formulation. Add **proton pump inhibitor** (or other acid-labile drug) typically in the amount equivalent to 10 doses (range=1 dose to 30 doses). Q.s. to 100 mL with distilled water. Different volumes of water may be added to achieve **proton pump inhibitor** concentrations ranging from 0.8 to 20 mg/mL.

Formulation 16: One Phase Lansoprazole 30 mg Tablet
Lansoprazole has a pKa of 4.1;. . . are not limited to, sodium bicarbonate, sodium carbonate,
dibasic sodium phosphate, and dipotassium phosphate.
Enough powder for 11 tablets is weighed out:

Proton pump inhibitor:
Lansoprazole powder 330 mg
Primary Essential Buffer(s):
Sodium bicarbonate USP 5500 mg
Dibasic sodium phosphate 2200 mg

DETD . . . limited to, sodium bicarbonate, sodium carbonate, disodium hydrogen phosphate (dibasic sodium phosphate), and dipotassium phosphate.
Enough powder for 11 tablets is weighed out:

Proton pump inhibitor:
Omeprazole powder USP 220 mg
Primary Essential Buffer(s):
Sodium bicarbonate USP 6500 mg
Magnesium oxide powder 1650 mg
Croscarmelose. . .

DETD . . . also be added.

Formulation 18: One Phase Omeprazole 40 mg Tablet

Enough powder for 11 tablets is weighed out:
Proton pump inhibitor:
Omeprazole powder USP 440 mg
Primary Essential Buffer(s):
Sodium bicarbonate USP 6500 mg

Magnesium oxide 1650 mg
Pregelatinized starch 500. . .
DETD . . . such as croscarmelose sodium and glidants such as magnesium stearate may additionally be used.

Formulation 19: Omeprazole Powder Formulations (single dose)

Proton pump inhibitor:
Omeprazole powder USP 20 mg or 40 mg
(or esomeprazole magnesium).
Primary Essential Buffer(s):
Sodium bicarbonate USP powder (60 micron) 1000 mg
Magnesium oxide. . .
DETD . . . with 5 mL to 20 mL distilled water at the time of use.

Formulation 23: Flavored Lansoprazole Powder (single dose)

Proton pump inhibitor:
Lansoprazole powder USP 30 mg
Primary Essential Buffer(s):
Dibasic Sodium Phosphate USP or 1500 mg
Sodium bicarbonate USP
Sucrose. . .
DETD . . . with 5 mL to 20 mL distilled water at the time of use.

Formulation 24: Unflavored Rabeprazole Powder (single dose)

Proton pump inhibitor:
Rabeprazole sodium powder USP 20 mg
Primary Essential Buffer(s):
Disodium phosphate duohydrate USP 2000 mg
Optional Secondary Essential. . .
DETD . . . rabeprazole sodium. This causes the rabeprazole sodium to remain insoluble thereby increasing its stability.

Formulation 25: Unflavored Rabeprazole Powder (single dose)

Proton pump inhibitor:
Rabeprazole sodium powder USP 20 mg
Primary Essential Buffer(s):
Sodium bicarbonate USP 1200 mg
Secondary Essential Buffer(s):
Trisodium phosphate USP 300 mg
Optional. . . Buffer(s):
Sodium hydroxide or Tribasic potassium may be added in higher or lower amounts to adjust pH for desired stability and additive **antacid** or buffering capacity.
DETD . . . formulation is designed to enable the use of the commercially available enteric-coated tablet of rabeprazole as the source of the **proton pump inhibitor**. This tablet requires disintegration prior to use as a liquid formulation. Part 1 (the low concentration of Secondary Essential Buffer). . . and simply added to the Primary Essential Buffer(s) (part 2) prior to use.

Formulation 26: Unflavored Rabeprazole Powder (single dose)

Proton pump inhibitor:
Rabeprazole sodium powder USP 20 mg
Primary Essential Buffer(s):
Calcium lactate USP 700 mg
Calcium glycerophosphate 700 mg
Secondary. . .

DETD . . . dissolving rabeprazole sodium delayed-release tablets (if used as a source of rabeprazole sodium).

Formulation 27: Unflavored Esomeprazole Powder (single dose)

Proton pump inhibitor:	
Esomeprazole magnesium powder USP	20 mg
Primary Essential Buffer(s):	
Calcium lactate USP	800 mg
Calcium glycerophosphate	800 mg
Secondary. . .	

DETD . . . a source of esomeprazole magnesium).

Formulation 28: Omeprazole Two Part Tablet
Two part tablets contain an outer buffer phase and inner buffer/**Proton pump inhibitor** core. Enough for 6 tablets is weighed out.

Inner Core:	
Proton pump inhibitor:	
Omeprazole powder USP	120 mg
(or esomeprazole magnesium or omeprazole sodium).	
Primary Essential Buffer(s):	
Sodium bicarbonate USP	1200 mg
Outer. . .	

DETD [0566] The outside layer surrounding the **proton pump inhibitor** tablet serves as a pH-buffering zone. Enough sodium bicarbonate for 6 tablets is weighed out with approximately 280 mg per. . .

DETD . . . sodium bicarbonate and magnesium oxide.

Formulation 29: Lansoprazole Two Part Tablet
Enough for 6 tablets is weighed out.

Inner Core:	
Proton pump inhibitor:	
Lansoprazole powder USP	180 mg
Primary Essential Buffer:	
Sodium bicarbonate USP	1200 mg
Outer Phase:	
Sodium bicarbonate USP	3960 mg

DETD . . . pregelatinized starch may be added.

Formulation 30: Pantoprazole Two Part Tablet
Enough for 6 tablets is weighed out.

Inner Core:	
Proton pump inhibitor:	
Pantoprazole powder USP	240 mg
(or pantoprazole sodium)	
Primary Essential Buffer:	
Sodium bicarbonate USP	1200 mg
Outer Phase:	
Sodium bicarbonate. . .	

DETD . . . may be added.

Formulation 31: Omeprazole or esomeprazole two part tablet.
Enough for 6 tablets is weighed out.

Inner Core:	
Proton pump inhibitor:	
Omeprazole powder USP (or esomeprazole or omeprazole sodium).	120 mg
Primary Essential Buffer:	

Sodium bicarbonate 1200 mg
Outer Phase:
Sodium. . .
DETD . . . added to enhance neutralization capacity.

Formulation 32: Lansoprazole Two part tablet
Enough for 6 tablets is weighed out.

Inner Core:
Proton pump inhibitor:
Lansoprazole powder USP 180 mg
Primary Essential Buffer:
Sodium bicarbonate 1200 mg
Outer Phase:
Sodium bicarbonate 3960 mg
DETD . . . added to enhance neutralization capacity.

Formulation 33: Pantoprazole Two part tablet
Enough for 6 tablets is weighed out.

Inner Core:
Proton pump inhibitor:
Pantoprazole sodium powder USP 240 mg
Primary Essential Buffer:
Sodium bicarbonate 1200 mg
Outer Phase:
Sodium bicarbonate 3960 mg
DETD . . . carbonate or others, may be added to enhance neutralization capacity.

Formulation 34: Omeprazole 20 mg Two-Part Tablet

Inner Core:
Proton pump inhibitor:
Omeprazole enteric coated granules (base, or sodium salt or esomeprazole sodium or magnesium) 20 mg
Outer Phase:
Sodium bicarbonate powder. . .
DETD . . . the inner core as described in Formulation 28. Other variations of this tablet include a uniform enteric coating surrounding the **proton pump inhibitor** of the inner core instead of separate enteric coated granules.

Formulation 35: Lansoprazole 30 mg Two-Part Tablet

Inner Core:
Proton pump inhibitor:
Lansoprazole enteric coated granules 30 mg
Outer Phase:
Sodium bicarbonate powder USP 1000 mg
DETD [0575] This two-part tablet is formulated as per Formulation 34.

Formulation 36: Rabeprazole 20 mg Two-Part Tablet

Inner Core:
Proton pump inhibitor:
Rabeprazole enteric coated granules 20 mg
Outer Phase:
Sodium bicarbonate powder USP 1000 mg
DETD . . . as in Formulation 28. The outer phase is combined with the inner core as in Formulation 28.

Formulation 38: Combination **Antacid** and Enteric Coated Dosage Form

Omeprazole enteric coated granules or enteric coated tablet	20	mg (or an equivalent dose of another **proton pump inhibitor**)
Calcium carbonate	1000	mg

DETD . . . in either a compressed tablet or in a larger capsule. In another embodiment, a capsule containing enteric coated granules of **proton pump inhibitor** can be placed within a larger capsule containing the calcium carbonate.

DETD . . . aluminum salts) because in many cases, sodium bicarbonate more quickly lowers gastric pH.

Formulation 39: Combination Rapid Release and Delayed Released **Proton Pump Inhibitor** and **Antacid**

Inner core:	
Omeprazole enteric coated granules or enteric coated tablet	10 or 20 mg (or an equivalent dose of another proton pump inhibitor)
Outer phase:	
Omeprazole powder	10 or 20 mg (or equivalent dose of another **proton pump inhibitor**)
Calcium Carbonate powder	1000 mg

DETD [0581] Formulation 40: Soft Chewable **Proton Pump Inhibitor**--Buffer Dosage Form

DETD [0582] Omeprazole 10 or 20 mg (or an equivalent dose of another **proton pump inhibitor**) is combined with the ingredients of a soft chewable **antacid** tablet (e.g., Viactiv®), which comprises calcium carbonate 500 or 1000 mg, corn syrup, sugar, chocolate non fat milk, cocoa butter,. . .

L20 ANSWER 22 OF 31 USPATFULL on STN
Full Text
AN 2003:152386 USPATFULL
TI Gastric retentive oral dosage form with restricted drug release in the lower gastrointestinal tract
IN Berner, Bret, El Granada, CA, UNITED STATES
Louie-Helm, Jenny, Union City, CA, UNITED STATES
PI US 2003104052 A1 20030605

DETD . . . drug is calcium carbonate, and which when incorporated into the dosage forms of the present invention becomes a non-systemic, controlled-release **antacid**. The dosage forms are also useful for delivering drugs continuously to the stomach that are only soluble in that portion. . . present invention are useful for the delivery of calcium carbonate or other calcium salts intended to be used as an **antacid** or as a dietary supplement to prevent osteoporosis. Calcium salts are soluble in the stomach but not in the remainder. . .

DETD . . . of (a) bismuth (e.g., as bismuth subsalicylate), (b) an antibiotic such as tetracycline, amoxicillin, thiamphenicol, or clarithromycin, and (c) a **proton pump inhibitor**, such as omeprazole. A combination of bismuth subsalicylate, thiamphenicol and omeprazole is a particularly preferred combination that may be delivered. . .

DETD [0205] FIG. 6 summarizes the data obtained with **bi-layer** and tri-layer ciprofloxacin HCl tablets. The **bi-layer** tablets contained an active layer and a 300-mg swelling layer (Polyox® 303). The tri-layer tablets contained active layers on the. . .

L20 ANSWER 25 OF 31 USPATFULL on STN
Full Text
AN 2002:69628 USPATFULL
TI Oral pharmaceutical dosage forms comprising a **proton pump inhibitor** and a NSAID
IN Depui, Helene, Goteborg, SWEDEN
Lundberg, Per, Molndal, SWEDEN
PI US 6365184 B1 20020402

TI Oral pharmaceutical dosage forms comprising a **proton pump inhibitor** and a NSAID

AB An oral pharmaceutical dosage form comprising an acid susceptible **proton pump inhibitor** and one or more NSAIDs in a fixed formulation, wherein the **proton pump inhibitor** is protected by an enteric coating layer. The fixed formulation is in the form of an enteric coating layered tablet,. . .

SUMM . . . of gastrointestinal disorders associated with the use of Non Steroidal Antiinflammatory Drugs (NSAIDs). The present preparations comprise an acid susceptible **proton pump inhibitor** in combination with one or more NSAID(s) in a new fixed unit dosage form, especially a tableted dosage form. Furthermore,. . .

SUMM Omeprazole being a well known **proton pump inhibitor** has been shown to be able to prevent gastric and duodenal erosions in healthy volunteers during treatment with acetyl salicylic. . .

SUMM . . . specific arrangement is taken to avoid degradation if the gastric acid inhibitor is an acid susceptible compound, such as a **proton pump inhibitor**.

SUMM In proposed therapies comprising NSAID(s) and an acid susceptible **proton pump inhibitor** the different active substances are administred separately. It is well known that patient compliance is a main factor in receiving. . .

SUMM . . . mentioned above. In respect of the stability properties, it is obvious that the one of the active substances being a **proton pump inhibitor** must be protected from contact with acidic gastric juice by an enteric coating layer. There are different enteric coating layered. . .

SUMM . . . Preparation of a multiple unit tableted dosage form arises specific problems when enteric coating layered pellets containing the acid susceptible **proton pump inhibitor** are compressed into tablets. If the enteric coating layer does not withstand the compression of the pellets into a tablet,. . .

SUMM The present invention provides oral, fixed unit dosage forms, i.e. multiple unit tableted dosage forms, enteric coating layered tablets, **multilayered** tablets or capsules filled with more than one pharmaceutically active compound. The active compounds are preferably an acid susceptible **proton pump inhibitor** in combination with one or more NSAIDs and wherein at least the **proton pump inhibitor** is protected by an enteric coated layer. These new dosage forms will simplify the regimen and improve the patient compliance.

DRWD FIG. 1 illustrates a cross-section of a multiple unit tableted dosage form comprising an acid susceptible **proton pump inhibitor** in the form of enteric coating layered pellets (1) in admixture with a fast disintegrating granulate comprising a NSAID (2).. . .

DRWD FIG. 2 illustrates a cross-section of a multiple unit tableted dosage form comprising an acid susceptible **proton pump inhibitor** in the form of enteric coating layered pellets (1) and a NSAID in the form of cyclodextrin complex (3) included. . .

DRWD FIG. 3 illustrates a cross-section of a tablet with two separate layers, one layer comprises an acid susceptible **proton pump inhibitor** in the form of enteric coating layered pellets (1) in admixture with excipients (5) and the other layer comprises a. . .

DRWD FIG. 4 illustrates a cross-section of a multiple unit tableted dosage form comprising an acid susceptible **proton pump inhibitor** in the form of enteric coating layered pellets (1) and a NSAID in the form of enteric coating layered pellets. . .

DRWD FIG. 5 illustrates a cross-section of an enteric coating layered tablet comprising an acid susceptible **proton pump inhibitor** (8) in admixture with one or more NSAID(s) (9) and excipients (5). The tablet is covered by an enteric coating. . .

DRWD FIG. 6 illustrates a tablet comprising an acid susceptible **proton pump inhibitor** in the form of enteric coating layered pellets (1) in admixture with a fast disintegrating granulate (4) in a tablet. . .

DETD . . . the invention is to provide an oral, multiple unit tableted dosage form comprising an anti-ulcer drug, preferably an acid susceptible **proton pump inhibitor** in the form of individually enteric coating layered units, together with one or more NSAIDs and tablet excipients compressed into a tablet. The enteric coating layer(s) covering the individual units of the acid susceptible **proton pump inhibitor** has properties such that the compression of the units into a tablet does not significantly affect the acid resistance of. . .

DETD Alternatively, the prepared tablet has separate layers, one layer that

comprises the acid susceptible **proton pump inhibitor** in the form of compressed enteric coated layered units and another layer that comprises the NSAID(s).

DETD Further alternatives are exemplified as multiple unit dosage forms wherein the **proton pump inhibitor** is in the form of individually enteric coating layered units and the NSAID(s) in the form of a) a complex. . . preparation with extended release of the NSAID(s), see FIG. 3. A further alternative is a multiple dosage form with the **proton pump inhibitor** in the form of individually enteric coating layered units compressed into a tablet and thereupon a separate layer of the. . .

DETD . . . alternative, the different active substances are dry mixed and filled into a capsule. In the latter preparation the acid susceptible **proton pump inhibitor** is in the form of enteric coating layered units and the NSAID(s) is/are in the form of granules or alternatively. . .

DETD The anti-ulcer drug is preferably an acid susceptible **proton pump inhibitor**. Such proton pump inhibitors are for example compounds of the general formula I ##STR1##

DETD A wide variety of NSAIDs may be used in combination with a suitable **proton pump inhibitor** and optional pharmaceutically acceptable excipients in the fixed unit dosage form according to the present invention. Such NASAIDs include for. . .

DETD The preferred multiple unit tableted dosage form comprising a **proton pump inhibitor** (in the form of a racemat, an alkaline salt or one of its single enantiomers) and one or more NSAIDs, is characterized in the following way. Individually enteric coating layered units (small beads, granules or pellets) containing the **proton pump inhibitor** and optionally containing alkaline reacting substances, are mixed with the NSAID(s) and conventional tablet excipients. Preferably, the NSAID(s) and tablet. . . "individual units" is meant small beads, granules or pellets, in the following referred to as pellets of the acid susceptible **proton pump inhibitor**.

DETD . . . tableted dosage form must not significantly affect the acid resistance of the enteric coating layered pellets comprising the acid susceptible **proton pump inhibitor**. In other words the mechanical properties, such as the flexibility and hardness as well as the thickness of the enteric. . .

DETD The acid resistance is defined as the amount of **proton pump inhibitor** in the tablets or pellets after being exposed to simulated gastric fluid USP, or to 0, 1 M HCl (aq). . . pellets to the medium. After two hours the enteric coating layered pellets are removed and analyzed for content of the **proton pump inhibitor** using High Performance Liquid Chromatography (HPLC).

DETD . . . core material for the individually enteric coating layered pellets can be constituted according to different principles. Seeds layered with the **proton pump inhibitor**, optionally mixed with alkaline substances, can be used as the core material for the further processing.

DETD The seeds which are to be layered with the **proton pump inhibitor** can be water insoluble seeds comprising different oxides, celluloses, organic polymers and other materials, alone or in mixtures or water-soluble. . . seeds comprising different inorganic salts, sugars, non-pareils and other materials, alone or in mixtures. Further, the seeds may comprise the **proton pump inhibitor** in the form of crystals, agglomerates, compacts etc. The size of the seeds is not essential for the present invention but may vary between approximately 0.1 and 2 mm. The seeds layered with the **proton pump inhibitor** are produced either by powder or solution/suspension layering using for instance granulation or spray coating layering equipment.

DETD Before the seeds are layered, the **proton pump inhibitor** may be mixed with further components. Such components can be binders, surfactants fillers, disintegrating agents, alkaline additives or other and/or. . .

DETD Alternatively, the **proton pump inhibitor** optionally mixed with alkaline substances and further mixed with suitable constituents can be formulated into a core material. Said core. . . preferably between 0.1 and 2 mm. The manufactured core material can be further be layered with additional ingredients comprising the **proton pump inhibitor** and/or be used for further processing.

DETD The **proton pump inhibitor** is mixed with pharmaceutical constituents to obtain preferred handling and processing properties and

a suitable concentration of the **proton pump inhibitor** in the final preparation. Pharmaceutical constituents such as fillers, binders, lubricants, disintegrating agents, surfactants and other pharmaceutically acceptable additives may. . .

DETD Further, the **proton pump inhibitor** may be mixed with an alkaline, pharmaceutically acceptable substance (or substances). Such substances can be chosen among, but are not. . . carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminium hydroxide/sodium bicarbonate coprecipitate; substances normally used in **antacid** preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $Al_{2O3}.6MgO.CO_{20}.12H_{2O}$, $(Mg_{6Al2}(OH)_{16CO3O}.4H_2)$, $MgO.Al_{2O3}.2Si O_2.nH_{20}$ or similar compounds;. . .

DETD . . . separate(s) the core material from the outer layers being enteric coating layer(s). This/these separating layers(s) protecting the core material of **proton pump inhibitor** should be water soluble or rapidly disintegrating in water.

DETD . . . layer(s) can be further strengthened by introducing into the layer(s) substances chosen from a group of compounds usually used in **antacid** formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds. . .

DETD . . . and to decrease diffusion of acidic gastric juices into the acid susceptible material. To protect the acid susceptible substance, the **proton pump inhibitor**, and to obtain an acceptable acid resistance of the dosage form according to the invention, the enteric coating layer(s) constitutes. . .

DETD . . . layer described above may also be used for an enteric coating layer of conventional tablets comprising a composition of a **proton pump inhibitor** and one or more NSAID(s), optionally the prepared tablet core also is covered by one of the separating layers described. . .

DETD The enteric coating layered pellets comprising a **proton pump inhibitor** are mixed with the granules comprising NSAID(s) and tablet excipients. The mixture is compressed into a multiple unit tableted dosage. . .

DETD Alternatively, the NSAID(s) may be dry mixed with the enteric coating layered pellets comprising the **proton pump inhibitor** optionally together with inactive excipients and compressed into tablets (direct compression), or the different active substances may be formulated in. . .

DETD Further, both the NSAID(s) and the **proton pump inhibitor** in the form of enteric coating layered pellets may be mixed with inactive tablet excipients and compressed into a tablet.. . .

DETD As a further alternative a multiple unit tableted dosage form comprising the **proton pump inhibitor** is spray coating layered by a suspension or solution comprising the NSAID(s). The prepared tablet is thereafter covered by a. . .

DETD . . . preferably less than 60%. By increasing the amount of the granules comprising the NSAID(s) the fraction of enteric coating layered **proton pump inhibitor** pellets in the multiple unit dosage form may be reduced. By choosing small enteric coating layered pellets in the formulation. . .

DETD . . . unit tablet formulation consists of enteric coating layered pellets containing one active substance in the form of an acid susceptible **proton pump inhibitor**, optionally mixed with alkaline reacting compound(s), compressed into tablet together with granules containing NSAID(s) and optionally tablet excipients. The addition of an alkaline reacting material to the **proton pump inhibitor** is not necessary, in any sense but such a substance may further enhance the stability of the **proton pump inhibitor** or some of the alkaline reacting compounds may react in situ with the enteric coating material to form a separating. . . media such as, for instance the liquids present in the proximal part of the small intestine, where dissolution of the **proton pump inhibitor** is desired. The NSAID(s) may be released in the stomach. The enteric coating layered pellets may further be covered with. . .

DETD . . . form represents a further aspect of the invention. After formulation of the pellets by spray coating or layering of the **proton pump inhibitor** onto seeds, or by extrusion/spheronization or granulation, e.g. rotor granulation of homogeneous pellets, the pellets

are first optionally covered with. . .

DETD . . . layer. The NSAID(s) may also be incorporated in a coating layer applied onto a multiple unit dosage form comprising the **proton pump inhibitor**, or the NSAID(s) and **proton pump inhibitor** in the form of enteric coating layered pellets are mixed with inactive tablet excipients and compressed into a multiple unit. . .

DETD . . . comprising the NSAID(s) may be in the form of a control release preparation. As a further alternative, the acid susceptible **proton pump inhibitor** in the form of enteric coating layered pellets may be filled in a capsule together with the NSAID(s) in the. . .

DETD . . . of the patients, the mode of administration and disease. In general each dosage form will comprise 0,1-200 mg of the **proton pump inhibitor** and 0,1-1000 mg of the NSAID(s). Preferably, each dosage form will comprise 10-80 mg of the **proton pump inhibitor** and 10-800 mg of the NSAID(s), and more preferably 10-40 mg of **proton pump inhibitor** and 10-500 mg of the NSAID(s), respectively. Especially preferred combinations comprise for instance 10 mg omeprazole together with 50 mg. . .

DETD **Two-layered** tablet dosage form with fast disintegrating part having 20 mg of lansoprazole in the form of enteric coated pellets comprised. . .

DETD . . . MCC and 18.2 mg of crosslinked polyvinylpyrrolidone per tablet, on top. These materials were then compressed together to give the **two-layered** tablets on a Diaf tableting machine equipped with 9X20 mm punches. Tablet hardness tested with a Schleuniger apparatus over the. . .

DETD The enteric coating layered pellets comprising a **proton pump inhibitor** may also be prepared as described in the following examples.

CLM What is claimed is:

. . . An oral pharmaceutical composition in the form of a multiple unit tablet comprising, as a first component, an acid susceptible **proton pump inhibitor**, and as a separate second component, at least one Non Steroidal Antiinflammatory Drug (NSAID), and as an optional third component,. . .

2. The composition according to claim 1, wherein the **proton pump inhibitor** is covered by a separating layer located underneath the enteric coating layer.

3. The composition according to claim 1, wherein the dosage form comprises an acid susceptible **proton pump inhibitor** and one NSAID.

4. The composition according to claim 1, wherein the **proton pump inhibitor** is omeprazole, an alkaline salt of omeprazole, a single enantiomer of omeprazole or an alkaline salt of the single enantiomer. . . .

5. The composition according to claim 4, wherein the **proton pump inhibitor** is S-omeprazole magnesium salt.

6. The composition according to claim 1, wherein the **proton pump inhibitor** is lansoprazole, a pharmaceutically acceptable salt of lansoprazole, a single enantiomer of lansoprazole or a pharmaceutically acceptable salt of the. . .

7. The composition according to claim 1, wherein the **proton pump inhibitor** is pantoprazole, a pharmaceutically acceptable salt of pantoprazole, a single enantiomer of pantoprazole or a pharmaceutically acceptable salt of the. . .

10. The composition according to claim 1, wherein the amount of **proton pump inhibitor** is in the range of 10-80 mg and the amount of the second component is in the range of 10-800. . .

11. The composition according to claim 1, wherein the amount of **proton pump inhibitor** is in the range of 10-40 mg and the amount of the second component is in the range of 10-500. . .

12. The composition according to claim 1, wherein the tableted dosage form comprises a first layer comprising a **proton pump inhibitor** and a separate second layer comprising the second component.

. . . tablet is dispersible to form an aqueous suspension comprising the second component and the enteric coating layered pellets of a **proton pump inhibitor**.

20. The composition according to claim 1, wherein the tablet core comprising the **proton pump inhibitor** is surrounded by a coating

layer comprising the second component.

. . . a composition in the form of a multiple unit tableted dosage form comprising, as a first component, an acid susceptible **proton pump inhibitor**, and as a separate second component, at least one Non-Steroidal Anti-Inflammatory Drug (NSAID), wherein the process comprises the steps of: (a) preparing the **proton pump inhibitor** in the form of enteric coating layered pellets; (b) mixing the enteric coated pellets with prepared granules comprising the second. . .
28. The composition according to claim 1, wherein the **proton pump inhibitor** is selected from the group consisting of the racemic form and a single enantiomer of each of omeprazole, lansoprazole, pantoprazole,. . .
30. The process according to claim 24 or 25, further comprising the step of covering the **proton pump inhibitor** with a separating layer before applying the enteric coating layer.

L20 ANSWER 26 OF 31 USPATFULL on STN
Full Text
AN 2001:18024 USPATFULL
TI Oral pharmaceutical dosage forms comprising a **proton pump inhibitor** and an **antacid** agent or alginate
IN Depui, Helene, Goteborg, Sweden
Hallgren, Agneta, Molndal, Sweden
PI US 6183776 B1 20010206
WO 9725066 19970717
TI Oral pharmaceutical dosage forms comprising a **proton pump inhibitor** and an **antacid** agent or alginate
AB An oral pharmaceutical dosage form comprising an acid susceptible **proton pump inhibitor** and one or more **antacid** agents or an alginate in a fixed formulation, wherein the **proton pump inhibitor** is protected by an enteric coating layer and an optional separating layer in between the **proton pump inhibitor** and the enteric coating. The fixed formulation is in the form of **multilayered** tablets, sachets or multiple unit tableted dosage forms. The multiple unit dosage form is most preferred. The new fixed formulation. . .
SUMM . . . pain/discomfort and heartburn. The present preparations comprise a combination of different gastric acid suppressing agents, such as an acid susceptible **proton pump inhibitor** and **antacid** agent(s) and/or an alginate in a new fixed unit dosage form, especially a tableted dosage form. Furthermore, the present invention. . .
SUMM **Antacid** agents and alginates may be used alone in the treatment of heartburn. They have a short duration of action but are seen as inexpensive and safe. **Antacid** agents work locally through a neutralisation of gastric acid. Alginates further give some mechanical protection against reflux or gastric acid into the oesophagasus. The main advantages of **antacid** agents and alginates are, that they provide fast relief of symtoms. The main disadvantage of **antacid** agents and alginates is that,. dosing has to be repeated frequently to keep the patients free of symtoms, further that. . .
SUMM EP 338861 describes a solid pharmaceutical preparation of an **antacid** and excipients. It is proposed to use this preparation in combination with a **proton pump inhibitor** or any other substance inhibit gastric acid secretion. There is no suggestion to combine these substances in one fixed unit. . .
SUMM U.S. Pat. No. 5,244,670 describes an ingestible pharmaceutical composition comprising a substance selected from the group consisting of **antacid** agents, acid secretion prevention agents, bismuth-containing agents, and mixtures thereof, and the excipient 3-1-menthoxy propane 1,2-diol. There are no specific. . . arrangements discussed in neither of these references, to solve the problem with one of the component being an acid susceptible **proton pump inhibitor.**
SUMM A combination therapy of a **proton pump inhibitor** and an **antacid** or an alginate would provide immediate symtom relief, provided by the local effect of the **antacid** agent or the alginate, combined with a long-lasting symtom resolution provided by the systemically acting **proton pump inhibitor**. Such a combination would be ideal for "on-demand treatment " of dyspepsia as well as for symtom resolution. The combination therapy comprising an acid suppressing agent, for instance a **proton pump inhibitor**, together with an **antacid** agent or an alginate could also be an alternative to each of them separately

in case of failure. It is. . .

SUMM . . . neutral media. In respect of the stability properties, it is obvious that the one of the active substances being a **proton pump inhibitor** must be protected from contact with acidic gastric juice by an enteric coating layer. There are different enteric coating layered. . .

SUMM . . . Preparation of a multiple unit tableted dosage form arises specific problems when enteric coating layered pellets comprising an acid susceptible **proton pump inhibitor** as active substance are compressed into tablets. If the enteric coating layer does not withstand the compression of the pellets. . .

SUMM . . . oral, fixed unit dosage forms, i.e. multiple unit tableted dosage forms, layered formulations comprising an enteric coating layered tablet core, **multilayered** tablets or a sachet filled with more than one pharmaceutically active compound. The active compounds present in the dosage form are preferably an acid susceptible **proton pump inhibitor** and **antacid** agents. Alternatively, in some of the formulations the **antacid** agents may be replaced by an alginate. These new dosage forms will simplify the regimen and improve the patient compliance.

DRWD FIG. 1 illustrates a cross-section of a multiple unit tableted dosage form comprising an acid susceptible **proton pump inhibitor** in the form of enteric coating layered pellets (1) in admixture with **antacid** agent(s) and pharmaceutical excipients(2). Optionally, the tablet is covered by a filmcoating layer, i.e. tablet coat (7).

DRWD . . . cross-section of a tablet with two separate layers, one of which comprising enteric coating layered pellets of an acid susceptible **proton pump inhibitor** (1) in admixture with excipients (3) and the other layer comprising a mixture of pharmaceutical excipients and an **antacid** agent(s) or an alginate (2). Optionally the layers are separated by an anti-tacking layer. Further the tablet is optionally covered. . .

DRWD FIG. 3 illustrates a cross-section of a tablet comprising a mixture of pharmaceutical excipients and an acid susceptible **proton pump inhibitor** in the tablet core (5) surrounded by of an enteric coating layer (8) optionally with a separating layer applied in between the tablet core and the enteric coating layer and upon the enteric coating layer a layer of the **antacid** agent(s) in admixture with pharmaceutical excipients 6). Optionally, the tablet is covered by a filmcoating layer (7).

DETD One object of the invention is to provide an oral, multiple unit tableted dosage form comprising an acid susceptible **proton pump inhibitor** in the form of individually enteric coating layered units together with one or more **antacid** agents in the form of a powder or granules compressed into a tablet. The enteric coating layer(s) covering the individual units of the acid susceptible **proton pump inhibitor** has properties such that the compression of the units into a tablet does not significantly affect the acid resistance of. . .

DETD . . . is divisible and easy to handle. Such a multiple unit tableted dosage form comprising enteric coating layered pellets of a **proton pump inhibitor** and **antacid** agent(s) also may be dispersed in a slightly acidic aqueous liquid and can be given to patients with swallowing disorders. . .

DETD Another object of the invention is to provide a tablet preparation comprising a **proton pump inhibitor** in admixture with tablet excipients in a tablet core and a separate layer surrounding the tablet core, which layer comprises one or more **antacid** agent(s) in admixture with pharmaceutical excipients compressed onto the tablet core. The tablet core is enteric coating layered before the surrounding layer comprising the **antacid** agents is applied. Optionally a separating layer is applied on the tablet core before the core is enteric coating layered.

DETD . . . the prepared tablet is sectioned in separate layers, each one comprising different active substances. One of the layers comprises the **proton pump inhibitor** in the form of enteric coating layered pellets in admixture with pharmaceutical excipients and the other layer(s) comprises(-e) the **antacid** agent(s)/alginate, respectively in admixture with pharmaceutical excipients. Optionally the **two layers** are separated by a separating layer to prevent tacking between the **two layers**.

DETD The new fixed unit dosage forms comprise as active substances one gastric acid suppressing agent, such as an acid susceptible **proton**

pump inhibitor, and **antacid** agent(s)/alginate. Alternatively, the **proton pump inhibitor** in the form of enteric coating layered pellets may be mixed with an alginate and optionally pharmaceutical excipients to be. . . of a multiple unit tableted dosage form containing enteric coating layered units comprising the active substance being an acid susceptible **proton pump inhibitor** and granules comprising the other active substance(s), i.e. the **antacid** agent(s) as shown in FIG. 1.

DETD The **antacid** agent(s) may preferably be formulated in preparations intended for instant release. Alternatively, the components may be formulated in an effervescent. . .

DETD The gastric acid suppressing agent is preferably an acid susceptible **proton pump inhibitor**. Such proton pump inhibitors are for example compounds of the general formula I ##STR1##

DETD The gastric acid suppressing agent is preferably an acid susceptible **proton pump inhibitor** but H_2 receptor antagonists such as ranitidine, cimetidine or famotidine may be used in the pharmaceutical compositions with an alginate as proposed in WO 95/017080 or together with **antacid** agent(s).

DETD A wide variety of **antacid** agent(s) and/or alginates may be used in combination with a suitable **proton pump inhibitor** in the fixed unit dosage form according to the present invention. Such **antacid** agents include for example aluminium hydroxide, calcium carbonate, magnesium hydroxide, magnesium carbonate and aluminium magnesium hydroxide carbonate (hydrotalcit) taken alone. . . an alginate selected from alginic acid or sodium alginate or other pharmaceutically acceptable alginate salts, hydrates, esters etc. Especially preferred **antacid** agents are magnesium or calcium based **antacid** agents and aluminium hydroxide/magnesium carbonate complex. Suitable **antacid** agents are for instance described in U.S. Pat. No. 5,409,709.

DETD The preferred multiple unit tableted dosage form comprising a **proton pump inhibitor** in the form of a racemat, an alkaline salt or one of its single enantiomers in combination with **antacid** agent(s), is characterized in the following way. Individually enteric coating layered units (small beads, granules or pellets) containing the acid susceptible **proton pump inhibitor** and optionally containing alkaline reacting substances, are mixed with the **antacid**(s) and conventionally tablet excipients. The **antacid**(s) and tablet excipients may be dry mixed or wet-mixed into granules. The mixture of enteric coating layered units, **antacid** agent(s) and optionally excipients are compressed into the multiple unit tableted dosage forms. With the expression "individual units" is meant small beads, granules or pellets, in the following referred to as pellets of the **proton pump inhibitor**.

DETD The acid resistance is defined as the amount of **proton pump inhibitor** in the tablets or pellets after being exposed to simulated gastric fluid USP, or to 0,1 M HCl (aq) relative. . . pellets to the medium. After two hours the enteric coating layered pellets are removed and analyzed for content of the **proton pump inhibitor** using High Performance Liquid Chromatography (HPLC).

DETD Core Material--for Enteric Coating Layered Pellets Comprising a **Proton Pump Inhibitor**

DETD . . . core material for the individually enteric coating layered pellets can be constituted according to different principles. Seeds layered with the **proton pump inhibitor**, optionally mixed with alkaline substances, can be used as the core material for the further processing.

DETD The seeds which are to be layered with the **proton pump inhibitor** can be water insoluble seeds comprising different oxides, celluloses, organic polymers and other materials, alone or in mixtures or water-soluble. . . seeds comprising different inorganic salts, sugars, non-pareils and other materials, alone or in mixtures. Further, the seeds may comprise the **proton pump inhibitor** in the form of crystals, agglomerates, compacts etc. The size of the seeds is not essential for the present invention but may vary between approximately 0.1 and 2 mm. The seeds layered with the **proton pump inhibitor** are produced either by powder or solution/suspension layering using for instance granulation or spray coating layering equipment.

DETD Before the seeds are layered, the **proton pump inhibitor** may be mixed with further components. Such components can be binders, surfactants fillers, disintegrating agents, alkaline additives or other and/or. . .

DETD Alternatively, the **proton pump inhibitor** optionally mixed with

alkaline substances and further mixed with suitable constituents can be formulated into a core material. Said core. . . and preferably between 0.1 and 2 mm. The manufactured core material can further be layered with additional ingredients comprising the **proton pump inhibitor** and/or be used for further processing.

DETD The **proton pump inhibitor** is mixed with pharmaceutical constituents to obtain preferred handling and processing properties and a suitable concentration of the substance in. . .

DETD Further, the **proton pump inhibitor** may also be mixed with an alkaline, pharmaceutically acceptable substance (or substances). Such substances can be chosen among, but are. . . carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminium hydroxide/sodium bicarbonate coprecipitate; substances normally used in **antacid** preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $Al_2O_3.6MgO.CO_2.12H_2O$, (Mg_6Al_2. . .

DETD . . . This/these separating layer(s), separate(s) the core material from the outer layers being enteric coating layer(s). The separating layer(s) protecting the **proton pump inhibitor** should be water soluble or rapidly disintegrating in water.

DETD . . . layer(s) can be further strengthened by introducing into the layer(s) substances chosen from a group of compounds usually used in **antacid** formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds. . .

DETD To protect the acid susceptible substance, the **proton pump inhibitor**, and to obtain an acceptable acid resistance of the dosage form according to the invention, the enteric coating layer(s) constitutes. . .

DETD . . . the enteric coating layer described above may also be used for enteric coating of conventional tablets comprising an acid susceptible **proton pump inhibitor**. Said enteric coating layered tablet is thereafter presscoated with **antacid** granules and pharmaceutical excipients.

DETD **Antacid** Agent(s) or Alginate Preparation

DETD The active substance in form of one or more **antacid** agent(s) are dry mixed with inactive excipients such as fillers, binders, disintegrants, and other pharmaceutically acceptable additives. The mixture is. . . are for instance mannitol, corn starch, potato starch, low substituted hydroxypropylcellulose, microcrystalline cellulose and crosslinked polyvinylpyrrolidone. The dry mixture comprising **antacid** agent(s) is mixed with a suitable granulation liquid comprising for instance hydroxypropylcellulose or polyvinylpyrrolidone dissolved in purified water or alcohol. . .

DETD Alternatively, the **antacid** agent(s) are dry mixed with pharmaceutically acceptable excipients according to the above. The alginate preparation should also be prepared by. . .

DETD The enteric coating layered pellets comprising a **proton pump inhibitor** are mixed with the prepared **antacid** granules or with the prepared dry mixture comprising the **antacid** agent(s). The mixture is admixed with lubricant(s) and compressed into a multiple unit tableted dosage form. Suitable lubricants for the. . .

DETD Further, the different active substances may be formulated into different layers, wherein the layer comprising the **proton pump inhibitor** preferably is in the form of a multiple unit tableted dosage form layered with the prepared mixture of the **antacid** agent(s) or an alginate preparation. The **two layers** may be separated by a third layer comprising antitacking agents.

DETD . . . weight of the total tablet weight and preferably less than 60%. By increasing the amount of the granules comprising the **antacid** agent(s) and excipients, the fraction of enteric coating layered pellets of the **proton pump inhibitor** may be reduced in the multiple unit tableted dosage form. By choosing small enteric coating layered pellets in the formulation. . .

DETD Thus, the preferred multiple unit tablet formulation consists of enteric coating layered pellets containing the acid susceptible **proton pump inhibitor**, optionally in admixture with alkaline reacting compound(s), compressed into tablets together with the prepared **antacid** mixture and optionally tablet excipients. The addition of an alkaline reacting material to the **proton pump inhibitor** is not necessary, in any sense, but such a substance may further enhance the stability of the **proton pump inhibitor** or some of the alkaline reacting compounds

may react in situ with the enteric coating material to form a separating. . . media such as, for instance the liquids present in the proximal part of the small intestine, where dissolution of the **proton pump inhibitor** is desired. The enteric coating layered pellets may further be covered with an overcoating layer before being formulated into the. . .

DETD . . . form represents a further aspect of the invention. After formulation of the pellets by spray coating or layering of the **proton pump inhibitor** onto seeds, or by extrusion/spheronization or granulation, e.g. rotor granulation of homogeneous pellets, the pellets are first optionally covered with. . . coating layer material. The coating is carried out as described above and in the accompanying examples. The preparation of the **antacid** mixture is also described above and in the examples. The pharmaceutical processes can preferably be completely water-based.

DETD The enteric coating layered pellets, with or without an over-coat, are mixed with the prepared **antacid** granules, tablet excipients and other pharmaceutically acceptable additives and compressed into tablets. Alternatively, the enteric coating layered pellets may be intimately mixed with tablet excipients and precompressed and further layered with the **antacid** or alginate preparation and finally compressed into a tablet. As a further alternative the **proton pump inhibitor** in form of a powder may be mixed with tablet excipients and compressed into a tablet which is optionally layered with a separating layer and thereafter enteric coating layered. Said tablet core is then presscoated with the **antacid** preparation. Finally the tablet may be covered by a tablet coat.

DETD As a further alternative, the **proton pump inhibitor** in the form of enteric coating layered pellets may be filled in a sachet together with an alginate optionally mixed. . .

DETD . . . of the patients, the mode of administration and disease. In general each dosage form will comprise 0.1-200 mg of the **proton pump inhibitor** and 0.1-1000 mg of the **antacid** agent(s)/alginate. Preferably, each dosage form will comprise 5-80 mg of the **proton pump inhibitor** and 100-900 mg of the **antacid** agent(s)/alginate, and more preferably 10-40 mg of **proton pump inhibitor** and 250-650 mg of the **antacid** agent(s)/alginate, respectively.

DETD Multiple unit tableted dosage form comprising magnesium omeprazole and **antacid** agents (batch size 400 tablets).

DETD . . . with 9X20 mm oval punches. The amount of omeprazole in each tablet was approx. 10 mg and the amount of **antacid** agents were approx. 500 mg in total. Tablet hardness was measured to 110N.

DETD Multiple unit tableted dosage form comprising magnesium omeprazole and **antacid** agents (batch size 500 tablets).

DETD . . . with 9X20 mm oval punches. The amount of omeprazole in each tablet was approx. 20 mg and the amount of **antacid** agents were approx. 500 mg in total. Tablet hardness was measured to 30-40N.

DETD Multiple unit tableted dosage form comprising S-omeprazole magnesium salt and **antacid** agents (batch size 500 tablets).

DETD . . . with 9X20 mm oval punches. The amount of S-omeprazole in each tablet was approx. 20 mg and the amount of **antacid** agents were approx. 500 mg in total. Tablet hardness was measured to 30N.

DETD The enteric coating layered pellets comprising a **proton pump inhibitor** may also be prepared as described in the following examples.

CLM What is claimed is:

1. An oral pharmaceutical composition comprising, as a first component, an acid susceptible **proton pump inhibitor**, and as a separate second component, at least one substance selected from the group consisting of **antacid** agents, alginates and mixtures thereof, and as an optional third component, pharmaceutically acceptable excipients, wherein: (a) the composition is in. . .

. . . multiple unit tableted dosage form having separate layers and comprising, as a first component in one layer, an acid susceptible **proton pump inhibitor**, and as a second component in a separate second layer, at least one substance selected from the group consisting of **antacid** agents, alginates and mixtures thereof, wherein the process comprises the steps of: (a) preparing the **proton pump inhibitor** in the form of enteric coating layered pellets; (b) mixing the enteric coated pellets with pharmaceutically acceptable excipients; (c) precompressing. . .

. . . a composition in the form of a multiple unit tableted dosage form comprising, as a first component, an acid susceptible **proton pump**

inhibitor, and as a separate second component, at least one substance selected from the group consisting of **antacid** agents, alginates and mixtures thereof, wherein the process comprises the steps of: (a) preparing the **proton pump inhibitor** in the form of enteric coating layered pellets; (b) mixing the enteric coated pellets with the second component; and (c). . .

4. The composition according to claim 1, wherein the **proton pump inhibitor** is covered by a separating layer located underneath the enteric coating layer.

5. The composition according to claim 1, wherein the tableted dosage form comprises an acid susceptible **proton pump inhibitor** and two **antacid** agents.

6. The composition according to claim 1, wherein the **proton pump inhibitor** is omeprazole, an alkaline salt of omeprazole, a single enantiomer of omeprazole or an alkaline salt of the single enantiomer.

. . .

7. The composition according to claim 6, wherein the **proton pump inhibitor** is S-omeprazole magnesium salt.

8. The composition according to claim 1, wherein the **proton pump inhibitor** is lansoprazole, an alkaline salt of lansoprazole, a single enantiomer of lansoprazole or an alkaline salt of the single enantiomer.

. . .

9. The composition according to any one of claims 6-8, wherein the **antacid** agents are aluminum hydroxide in combination with magnesium or aluminum carbonate.

10. The composition according to any one of claims 6-8, wherein the **antacid** agents are calcium hydroxide in combination with magnesium or calcium carbonate.

11. The composition according to claim 1, wherein the amount of the **proton pump inhibitor** is in the range of 5-80 mg, and the amount of the second component is in the range of 100-900. . .

12. The composition according to claim 1, wherein the amount of the **proton pump inhibitor** is in the range of 10-40 mg, and the amount of the second component is in the range of 250-650. . .

13. The composition according to claim 1, wherein the tableted dosage form comprises a first layer comprising the **proton pump inhibitor** and a separate second layer comprising the second component.

. . . tablet is dispersible to form an aqueous suspension comprising the second component and the enteric coating layered pellets comprising a **proton pump inhibitor**.

22. The composition according to claim 1, wherein the **proton pump inhibitor** is in the form of a multiple unit tableted dosage form layered with a coating layer comprising the second component.

. . .

23. The composition according to claim 1, wherein the **proton pump inhibitor** is selected from the group consisting of the racemic form and a single enantiomer of each of omeprazole, lansoprazole, pantoprazole,. . .

25. The process according to claim 3, further comprising the step of: covering the **proton pump inhibitor** with a separating layer before applying the enteric coating layer.

26. The composition according to claim 1, wherein the second component is a mixture of an **antacid** and alginate.

27. The composition according to any one of claims 6-8, wherein the **antacid** agents are magnesium hydroxide in combination with aluminum carbonate, magnesium carbonate or calcium carbonate.

L20 ANSWER 27 OF 31 USPATFULL on STN
Full Text
AN 2000:141911 USPATFULL
TI Oral pharmaceutical dosage form
IN Depui, Helene, Goteborg, Sweden

Rosinski, Adam, Molndal, Sweden

PI US 6136344 20001024
WO 9624375 19960815

AB An oral pharmaceutical dosage form comprising an acid susceptible **proton pump inhibitor** and one or more antibacterial compounds in a fixed formulation. The fixed formulation is intended for oral use and in. . .

SUMM . . . preparations especially for use in the treatment of disorders associated with Helicobacter infections. The present preparations comprise an acid susceptible **proton pump inhibitor** in combination with one or more antibacterial compounds in a new fixed unit dosage form, especially a tableted dosage form.. . .

SUMM . . . Some of these therapies also comprise a bismuth compound, see for instance WO 89/03219 (Borody). Other combination therapies comprise a **proton pump inhibitor** and one or more antibacterial compounds, for instance a combined regimen of omeprazole and amoxicillin which has been approved by. . .

SUMM . . . and neutral media. In respect of the stability properties, it is obvious that one of the active substances being a **proton pump inhibitor** must be protected from contact with acidic gastric juice by an enteric coating layer. There are different enteric coating layered. . .

SUMM The present invention provides oral, fixed unit dosage forms, i.e. multiple unit tableted dosage forms, enteric coating layered tablets, **multilayered** tablets or a capsule filled with more than one pharmaceutically active compound. The active compounds present are preferably an acid susceptible **proton pump inhibitor** and one or more antibacterial substances. These new dosage forms will simplify the regimen and improve the patient compliance.

DRWD FIG. 1 illustrates a cross-section of a multiple unit tableted dosage form comprising an acid susceptible **proton pump inhibitor** in the form of enteric coating layered pellets (1) in admixture with an antibacterial granulation (2). The tablet is covered. . .

DRWD . . . a cross-section of a tablet with two separate layers, one layer comprises enteric coating layered pellets of an acid susceptible **proton pump inhibitor** (1) in admixture with excipients (3) and the other layer comprises the antibacterial compound(s) (2). The tablet is covered by. . . .

DRWD FIG. 3 illustrates a cross-section of an enteric coating layered tablet comprising an acid susceptible **proton pump inhibitor** in admixture with one or more antibacterial substances (4). The tablet is covered by an enteric coating layer (7).

DRWD FIG. 4 illustrates an enteric coating layered tablet consisting of two separate layers, one layer comprises an acid susceptible **proton pump inhibitor** (5) and the other layer comprises the antibacterial compound(s) (6).

DETD One object of the invention is to provide an oral, multiple unit tableted dosage form comprising an acid susceptible **proton pump inhibitor** in the form of individually enteric coating layered units together with one or more antibacterial compounds in the form of. . . a powder or granules compressed into a tablet. The enteric coating layer(s) covering the individual units of the acid susceptible **proton pump inhibitor** has properties such that the compression of the units into a tablet does not significantly affect the acid resistance of. . . the prepared tablet has separate layers, one layer is in the form of compressed enteric coated layered units comprising the **proton pump inhibitor** and another layer comprises the antibacterial compound(s).

DETD . . . dosage form comprising enteric coating layered units of the one of the active substance which is acid susceptible, i.e. the **proton pump inhibitor**, and granules of the other active substance(s), i.e. the antibacterial granulation, as shown in FIGS. 1 and 2. Alternatively, the. . . alternative, the different active substances are dry mixed and filled into a capsule. In the latter preparation the acid susceptible **proton pump inhibitor** is in the form of enteric coating layered units (1).

DETD Another object of the invention is to provide a tablet preparation comprising an acid susceptible **proton pump inhibitor** in admixture with one or more antibacterial substances compressed into a tablet, which tablet is enteric coating layered. Optionally a. . . prepared tablet core has separate layers, each one comprising different active substances. One of the layers comprises the acid susceptible **proton pump inhibitor** and another layer(s) comprises(-e) the antibacterial

substance or substances, respectively. The prepared tablet is thereafter enteric coating layered.

DETD Furthermore, the present invention provides a capsule preparation comprising the acid susceptible **proton pump inhibitor** in the form of enteric coating layered pellets mixed with one or more antibacterial compounds in the form of granules. . .

DETD The new fixed unit dosage forms comprise as active substances an acid susceptible **proton pump inhibitor** and one or more antibacterial compounds. The different active components used in the dosage forms are defined below.

DETD A wide variety of antibacterial compounds may be used in combination with a suitable **proton pump inhibitor** in the fixed unit dosage form according to the present invention. Such antibacterial compounds include for example nitroiridazole antibiotics, tetracyclines,. . .

DETD The preferred multiple unit tableted dosage form comprising a **proton pump inhibitor** in the form of a racemat, an alkaline salt or one of its single enantiomers and one or more antibacterial. . . is characterized in the following way. Individually enteric coating layered units (small beads, granules or pellets) containing the acid susceptible **proton pump inhibitor** and optionally containing alkaline reacting substances, are mixed with the antibacterial compound(s) and conventional tablet excipients. Preferably, the antibacterial compound(s). . . the expression "individual units" is meant small beads, granules or pellets, in the following referred to as pellets of the **proton pump inhibitor**.

DETD The acid resistance is defined as the amount of **proton pump inhibitor** in the tablets or pellets after being exposed to simulated gastric fluid USP, or to 0.1 M HCl (aq) relative. . . pellets to the medium. After two hours the enteric coating layered pellets are removed and analyzed for content of the **proton pump inhibitor** using High Performance Liquid Chromatography (HPLC).

DETD Core Material--for Enteric Coating Layered Pellets Comprising a **Proton Pump Inhibitor**

DETD . . . for the individually enteric coating layered pellets can be constituted according to different principles. Seeds layered with the acid susceptible **proton pump inhibitor**, optionally mixed with alkaline substances, can be used as the core material for the further processing.

DETD The seeds which are to be layered with the acid susceptible **proton pump inhibitor** can be water insoluble seeds comprising different oxides, celluloses, organic polymers and other materials, alone or in mixtures or water-soluble. . . seeds comprising different inorganic salts, sugars, non-pareils and other materials, alone or in mixtures. Further, the seeds may comprise the **proton pump inhibitor** in the form of crystals, agglomerates, compacts etc. The size of the seeds is not essential for the present invention but may vary between approximately 0.1 and 2 mm. The seeds layered with the **proton pump inhibitor** are produced either by powder or solution/suspension layering using for instance granulation or spray coating layering equipment.

DETD Before the seeds are layered, the **proton pump inhibitor** may be mixed with further components. Such components can be binders, surfactants, fillers, disintegrating agents, alkaline additives or other and/or. . .

DETD Alternatively, the **proton pump inhibitor** optionally mixed with alkaline substances and further mixed with suitable constituents can be formulated into core material. Said core material. . . and preferably between 0.1 and 2 mm. The manufactured core material can further be layered with additional ingredients comprising the **proton pump inhibitor** and/or be used for further processing.

DETD The **proton pump inhibitor** is mixed with pharmaceutical constituents to obtain preferred handling and processing properties and a suitable concentration of the substance in. . .

DETD Further, the **proton pump inhibitor** may also be mixed with an alkaline, pharmaceutically acceptable substance (or substances). Such substances can be chosen among, but are. . . carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminium hydroxide/sodium bicarbonate coprecipitate; substances normally used in **antacid** preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $Al_2O_3.6MgO.CO_2.12H_2O$, (Mg_6Al_2. . .

DETD . . . layer(s) can be further strengthened by introducing into the

layer(s) substances chosen from a group of compounds usually used in **antacid** formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds. . .

DETD To protect the acid susceptible substance, the **proton pump inhibitor**, and to obtain an acceptable acid resistance of the dosage form according to the invention, the enteric coating layer(s) constitutes. . .

DETD . . . layer described above may be used for enteric coating layering of conventional tablets comprising a composition of an acid susceptible **proton pump inhibitor** and one or more antibacterial compounds, optionally covered by one of the separating layers described above. As a further alternative, the **proton pump inhibitor** may be replaced in such a tablet by another gastric acid suppressing agents, such as a H_2 -receptor antagonist, for. . .

DETD The enteric coating layered pellets comprising a **proton pump inhibitor** are mixed with the granules comprising antibacterial compounds and tablet excipients. The dry mixture is compressed into a multiple unit. . .

DETD . . . unit tablet formulation consists of enteric coating layered pellets containing one active substance in the form of an acid susceptible **proton pump inhibitor**, optionally mixed with alkaline reacting compound(s), compressed into tablet together with a granulation containing antibacterial compound(s) and optionally tablet excipients. The addition of an alkaline reacting material to the **proton pump inhibitor** is not necessary, in any sense but such a substance may further enhance the stability of the **proton pump inhibitor** or some of the alkaline reacting compounds may react in situ with the enteric coating material to form a separating. . . media such as, for instance the liquids present in the proximal part of the small intestine, where dissolution of the **proton pump inhibitor** is desired. The antibacterial substance(s) may be released in the stomach. The enteric coating layered pellets may further be covered. . .

DETD . . . form represents a further aspect of the invention. After formulation of the pellets by spray coating or layering of the **proton pump inhibitor** onto seeds, or by extrusion/spheronization or granulation, e.g. rotor granulation of homogeneous pellets, the pellets are first optionally covered with. . .

DETD . . . tablet excipients and other pharmaceutical acceptable additives and compressed into tablets. The tablet may be in the form of a **two layer** tablet, wherein one layer comprises the enteric coating layered pellets optionally mixed with inactive excipients and the other layer comprises. . . before applying an optional separating layer and an enteric coating layer. The tablet may be in the form of a **two layer** enteric coating layered tablet, wherein one layer comprises one of the active substances and the other layer comprises the other active substance(s). As a further alternative, the **proton pump inhibitor** in the form of enteric coating layered pellets may be filled in a capsule together with the antibacterial substance(s) in. . .

DETD . . . of the patients, the mode of administration and disease. In general each dosage form will comprise 0.1-200 mg of the **proton pump inhibitor** and 0.1 mg-1.2 g of the antibacterial compound(s). Preferably, each dosage form will comprise 10-80 mg of the **proton pump inhibitor** and 100-900 mg of the antibacterial compound(s), and more preferably 20-40 mg of **proton pump inhibitor** and 250-650 mg of the antibacterial compound(s), respectively.

CLM What is claimed is:

. . . consisting essentially of, as a first component, at least one antibacterial compound, and as a second component, an acid susceptible **proton pump inhibitor**, wherein: (a) the composition is in the form of a multiple unit tablet; (b) the **proton pump inhibitor** is in the form of pellets covered with an enteric coating polymer layer; (c) the first component is separated from the **proton pump inhibitor** by the enteric coating layer covering the second component; and (d) the enteric coating layer has mechanical properties such that. . .

5. The composition of claim 1, wherein the **proton pump inhibitor** is omeprazole or a pharmaceutically acceptable salt of omeprazole.

6. The composition of claim 1, wherein the **proton pump inhibitor** is omeprazole, an alkaline salt of omeprazole, a (-)-enantiomer of omeprazole or an alkaline salt of the (-)-enantiomer of omeprazole.

. . .

7. The composition of claim 1, wherein the **proton pump inhibitor** is S-omeprazole magnesium salt.

8. The composition of claim 1, wherein the **proton pump inhibitor** is lansoprazole, a pharmaceutically acceptable salt of lansoprazole, a single enantiomer of lansoprazole or a pharmaceutically acceptable salt of the. . .

. . . 1, wherein the amount of the antibacterial component is in the range of 100-900 mg and the amount of the **proton pump inhibitor** is in the range of 10-80 mg.

. . . wherein the amount of the first antibacterial component is in the range of 250-650 mg and the amount of the **proton pump inhibitor** is in the range of 20-40 mg.

14. The composition of claim 13, wherein the acid susceptible **proton pump inhibitor** is located in one layer and wherein the antibacterial component is located in the other layer.

16. The composition of claim 1, wherein the **proton pump inhibitor** is covered by a separating layer located underneath the enteric coating layer.

. . . consisting essentially of, as a first component, at least one antibacterial compound, and as a second component, an acid susceptible **proton pump inhibitor**, wherein the process comprises the steps of: (a) preparing the **proton pump inhibitor** in the form of enteric coating layered pellets; (b) mixing the enteric coated pellets with a prepared granules of the. . .

L20 ANSWER 28 OF 31 USPATFULL on STN
Full Text
AN 2000:137861 USPATFULL
TI Oral pharmaceutical dosage forms comprising a **proton pump inhibitor** and a prokinetic agent
IN Depui, Helene, Goteborg, Sweden
Hallgren, Agneta, Molndal, Sweden
PI US 6132771 20001017
WO 9725065 19970717
TI Oral pharmaceutical dosage forms comprising a **proton pump inhibitor** and a prokinetic agent
AB An oral pharmaceutical dosage form comprising a **proton pump inhibitor** and one or more prokinetic agents in a fixed formulation, wherein the **proton pump inhibitor** is protected by an enteric coating layer. The fixed formulation is in the form of **multilayered** tablets, capsules or multiple unit tableted dosage forms. The multiple unit dosage forms are most preferred. The new fixed formulation. . .
SUMM . . . treatment of disorders associated with gastro oesophageal reflux. The present preparations comprise a gastric acid suppressing agent, such as a **proton pump inhibitor**, in combination with one or more prokinetic agents in a new fixed unit dosage form, especially a tablet. Furthermore, the. . .
SUMM . . . In respect of the stability properties, it is obvious that the one of the active substances being an acid susceptible **proton pump inhibitor** must be protected from contact with acidic gastric juice by an enteric coating layer. There are different enteric coating layered. . .
SUMM The present invention provides oral, fixed unit dosage forms, i.e. a multiple unit tableted dosage forms, **multilayered** tablets or a capsule filled with more than one pharmaceutically active compound. The active compounds present in the dosage form are preferably an acid susceptible **proton pump inhibitor** which is protected by an enteric coating layer, and one or more prokinetic agents. These new dosage forms will simplify. . .
DRWD FIG. 1 illustrates a cross-section of a multiple unit tableted dosage form comprising an acid susceptible **proton pump inhibitor** in the form of enteric coating layered pellets (1) in admixture with a prokinetic agent and pharmaceutically acceptable excipients (2).. . .
DRWD FIG. 3 illustrates a cross-section of an enteric coating layered tablet comprising a **proton pump inhibitor** in admixture with pharmaceutically acceptable excipients in the tablet core (5) surrounded by an enteric coating layer (8) and thereupon. . .

DRWD FIG. 4 illustrates a cross-section of a multiple unit tableted dosage form comprising an acid susceptible **proton pump inhibitor** in the form of enteric coating layered pellets (1) in admixture with excipients (3) and on the multiple unit tableted. . .

DETD One object of the invention is to provide an oral, multiple unit tableted dosage form comprising an acid susceptible **proton pump inhibitor** in the form of individually enteric coating layered units together with one or more prokinetic agents in the form of a powder or granules compressed into a tablet. The enteric coating layer(s) covering the individual units of the **proton pump inhibitor** has properties such that the compression of the units into a tablet does not significantly affect the acid resistance of. . .

DETD The **proton pump inhibitor**, in the form of enteric coating layered units, may also be mixed with pharmaceutically acceptable excipients and compressed into a. . .

DETD Another object of the invention is to provide a tablet preparation comprising a **proton pump inhibitor** in admixture with tablet excipients in a tablet core and a separate layer surrounding the tablet core, which layer comprises. . .

DETD Alternatively, the prepared tablet is sectioned in separate layers, each one comprising different active substances. Preferably one layer comprises the **proton pump inhibitor** in the form of enteric coating layered pellets in admixture with pharmaceutically acceptable excipients and another layer(s) comprises(-e) the prokinetic. . .

DETD Furthermore, the present invention provides a capsule preparation comprising the **proton pump inhibitor** in the form of enteric coating layered pellets mixed with one or more prokinetic agents in the form of prepared. . . The new fixed unit dosage forms comprise as active substances one gastric acid suppressing agent, such as an acid susceptible **proton pump inhibitor** and one or more prokinetic agents. The different therapeutically active components used in the dosage forms are defined below.

DETD The gastric acid suppressing agent is preferably an acid susceptible **proton pump inhibitor**. Such proton pump inhibitors are for example compounds of the general formula I ##STR1## wherein ##STR2## wherein N in the. . .

DETD The gastric acid suppressing agent is preferably an acid susceptible **proton pump inhibitor** but other gastric acid suppressing agents such as the H_2 receptor antagonists: ranitidine, cimetidine or famotidine, may be used together. . .

DETD A wide variety of prokinetic compounds may be used in combination with a suitable **proton pump inhibitor** in the fixed unit dosage form according to the present invention. Such prokinetic agents include for example cisapride, mosapride, metoclopramide,. . .

DETD The preferred multiple unit tableted dosage form comprising a **proton pump inhibitor** in the form of a racemate, an alkaline salt or one of its single enantiomers in combination with a prokinetic compound, is characterized in the following way. Individually enteric coating layered units (small beads, granules or pellets) containing the **proton pump inhibitor** and optionally alkaline reacting substances, are mixed with the prokinetic compound and conventionally tablet excipients. The prokinetic compound and tablet. . . the expression "individual units" is meant small beads, granules or pellets, in the following referred to as pellets of the **proton pump inhibitor**.

DETD The acid resistance is defined as the amount of **proton pump inhibitor** in the tablets or pellets after being exposed to simulated gastric fluid USP, or to 0.1 M HCl (aq) relative. . . pellets to the medium. After two hours the enteric coating layered pellets are removed and analyzed for content of the **proton pump inhibitor** using High Performance Liquid Chromatography (HPLC).

DETD Core material--for Enteric Coating Layered Pellets Comprising a **Proton Pump Inhibitor**

DETD . . . core material for the individually enteric coating layered pellets can be constituted according to different principles. Seeds layered with the **proton pump inhibitor**, optionally mixed with alkaline substances, can be used as the core material for the further processing.

DETD The seeds which are to be layered with the **proton pump inhibitor** can be water insoluble seeds comprising different oxides, celluloses, organic polymers and other materials, alone or in mixtures or water-soluble. . . seeds comprising different inorganic salts, sugars, non-pareils and other materials, alone or in mixtures. Further,

the seeds may comprise the **proton pump inhibitor** in the form of crystals, agglomerates, compacts etc. The size of the seeds is not essential for the present invention but may vary between approximately 0.1 and 2 mm. The seeds layered with the **proton pump inhibitor** are produced either by powder or solution/suspension layering using for instance granulation or spray coating layering equipment.

DETD Before the seeds are layered, the **proton pump inhibitor** may be mixed with further components. Such components can be binders, surfactants fillers, disintegrating agents, alkaline additives or other and/or. . .

DETD Alternatively, the **proton pump inhibitor** optionally mixed with alkaline substances and further mixed with suitable constituents can be formulated into a core material. Said core. . . and preferably between 0.1 and 2 mm. The manufactured core material can further be layered with additional ingredients comprising the **proton pump inhibitor** and/or be used for further processing.

DETD The **proton pump inhibitor** is mixed with pharmaceutical constituents to obtain preferred handling and processing properties and a suitable concentration of the substance in. . .

DETD Further, the **proton pump inhibitor** may also be mixed with an alkaline, pharmaceutically acceptable substance (or substances). Such substances can be chosen among, but are. . . carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminium hydroxide/sodium bicarbonate coprecipitate; substances normally used in **antacid** preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $Al_2O_3.6MgO.CO_2.12H_2O$, (Mg_6Al_2. . .

DETD . . . the core material from the outer layers being enteric coating layer(s). The separating layer(s) protecting the core material of a **proton pump inhibitor** should be water soluble or rapidly disintegrating in water.

DETD . . . layer(s) can be further strengthened by introducing into the layer(s) substances chosen from a group of compounds usually used in **antacid** formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds. . .

DETD To protect the acid susceptible substance, the **proton pump inhibitor**, and to obtain an acceptable acid resistance of the dosage form according to the invention, the enteric coating layer(s) constitutes. . .

DETD Alternatively the enteric coating layer described above may be used for enteric coating of conventional tablets comprising an acid susceptible **proton pump inhibitor**. Said enteric coating layered tablet is thereafter presscoated with a granulation comprising the prokinetic compound.

DETD . . . can be applied in a separate layer onto a multiple unit tableted dosage form or surrounding the tablet comprising the **proton pump inhibitor**. The prokinetic agent(s) is dispersed or dissolved in an aqueous solution optionally comprising binders for suspension layering onto the tablet.

DETD The enteric coating layered pellets comprising a **proton pump inhibitor** are mixed with the granules comprising prokinetic compound and tablet excipients such as fillers, binders, disintegrants, lubricants and other pharmaceutically. . .

DETD Further, the different active substances may be formulated into different layers, wherein the layer comprising the **proton pump inhibitor** is in the form of a multiple unit tableted dosage form layered with prepared prokinetic granules. The **two layers** may be separated by an anti-tacking layer.

DETD As a further alternative the **proton pump inhibitor** is dry mixed with inactive excipients and compressed into a conventional tablet which is coating layered with an enteric coating. . . with a prokinetic preparation. The tablet core may also be formulated as a multiple unit tableted dosage form comprising the **proton pump inhibitor**, the tablet is spray coating layered by a suspension comprising the prokinetic agent(s).

DETD . . . By increasing the amount of the granules comprising the prolinetic agent the fraction of enteric coating layered pellets of the **proton pump inhibitor** may be reduced in the multiple unit tableted dosage form. By choosing small enteric coating layered pellets in the formulation. . .

DETD . . . preferred multiple unit tablet formulation consists of enteric

coating layered pellets containing one active substance in the form of a **proton pump inhibitor**, optionally admixed with alkaline reacting compound(s), compressed into tablets together with the prepared prokinetic mixture and optionally tablet excipients. The addition of an alkaline reacting material to the **proton pump inhibitor** is not necessary, in any sense but such a substance may further enhance the stability of the **proton pump inhibitor** or some of the alkaline reacting compounds may react in situ with the enteric coating material to form a separating. . . media such as, for instance the liquids present in the proximal part of the small intestine, where dissolution of the **proton pump inhibitor** is desired. The prokinetic agent(s) may be released in the stomach. The enteric coating layered pellets may further be covered. . .

DETD . . . form represents a further aspect of the invention. After formulation of the pellets by spray coating or layering of the **proton pump inhibitor** onto seeds, or by extrusion/spheronization or granulation, e.g. rotor granulation of homogeneous pellets, the pellets are first optionally covered with. . .

DETD . . . precompressed and further layered with the prepared prokinetic mixture and finally compressed into a tablet. As a further alternative the **proton pump inhibitor** in form of the active substance may be mixed with tablet excipients and compressed into a tablet which is optionally. . . layered. Said tablet is then presscoated with the prepared prokinetic mixture. Alternatively, a multiple unit tableted dosage form of the **proton pump inhibitor** is manufactured as describes above. The multiple unit dosage form is spray coating layered by an aqueous suspension comprising the. . . prokinetic agent(s). The suspension may optionally comprise binders; such as hydroxypropyl methylcellulose, and an alcohol to solve the binder. The **proton pump inhibitor** in the form of enteric coating layered pellets may also be filled into a capsule together with the prokinetic substance. . .

DETD . . . of the patients, the mode of administration and disease. In general each dosage form will comprise 0.1-200 mg of the **proton pump inhibitor** and 0.1-100 mg of the prokinetic compound. Preferably, each dosage form will comprise 10-80 mg of the **proton pump inhibitor** and 3-80 mg of the prokinetic compound, and more preferably 10-40 mg of **proton pump inhibitor** and 15-40 mg of the prokinetic compound, respectively.

DETD . . . water purified. The granulation is dried and milled through sive 1 mm in a suitable mill. The prepared granules comprising **proton pump inhibitor** is mixed with talc, microcrystalline cellulose and sodium stearyl fumarate and compressed into tablets using a rotary tableting machine equipped. . .

DETD The enteric coating layered pellets comprising a **proton pump inhibitor** may also be prepared as described in the following examples.

CLM What is claimed is:

1. An oral pharmaceutical composition comprising, as a first component, an acid susceptible **proton pump inhibitor**, and as a separate second component, at least one prokinetic agent, and as an optional third component, pharmaceutically acceptable excipients,. . .

2. The composition according to claim 1, wherein the **proton pump inhibitor** is covered by a separating layer located underneath the enteric coating layer.

3. The composition according to claim 1, wherein the tableted dosage form comprises a **proton pump inhibitor** and one prokinetic agent.

4. The composition according to claim 1, wherein the **proton pump inhibitor** is omeprazole, an alkaline salt of omeprazole, a single enantiomer of omeprazole or an alkaline salt of the single enantiomer.

. . .

5. The composition according to claim 4, wherein the **proton pump inhibitor** is S-omeprazole magnesium salt.

6. The composition according to claim 1, wherein the **proton pump inhibitor** is lansoprazole, an alkaline salt of lansoprazole, a single enantiomer of lansoprazole or an alkaline salt of the single enantiomer.

. . .

9. The composition according to claim 1, wherein the amount of the **proton pump inhibitor** is in the range of 10-80 mg, and the amount of the second component is in the range of 3-80. . .

10. The composition according to claim 1, wherein the amount of the

proton pump inhibitor is in the range of 10-40 mg, and the amount of the second component is in the range of 15-40. . .
11. The composition according to claim 1, wherein the tableted dosage form comprises a first layer comprising the **proton pump inhibitor** and a separate second layer comprising the second component.

. . . is dispersible to form a slightly acidic aqueous suspension comprising the second component and the enteric coating pellets comprising a **proton pump inhibitor**.

18. The composition according to claim 1, wherein the **proton pump inhibitor** is in the form of a multiple unit dosage form layered with a coating layer comprising the second component.

. . . manufacture of a composition in the form of a multiple unit tableted dosage form comprising, as a first component, a **proton pump inhibitor**, and as a separate second component, at least one prokinetic agent, comprising the steps of (a) preparing the **proton pump inhibitor** in the form of enteric coating layered pellets; (b) mixing the enteric coated pellets with the second component and an. . .
. . . of a multiple unit tableted dosage form having separate layers and comprising, as a first component in one layer a **proton pump inhibitor**, and as a second component in a separate second layer, at least one prokinetic agent, comprising the steps of: (a) preparing the **proton pump inhibitor** in the form of enteric coating layered pellets; (b) mixing the enteric coated pellets with pharmaceutically acceptable tablet excipients; (c). . .

L20 ANSWER 30 OF 31 USPAT2 on STN
Full Text
AN 2002:279721 USPAT2
TI Oral pharmaceutical dosage forms comprising a **proton pump inhibitor** and a NSAID
IN Depui, Helene, Goteborg, SWEDEN
Lundberg, Per, Molndal, SWEDEN
PI US 6613354 B2 20030902
TI Oral pharmaceutical dosage forms comprising a **proton pump inhibitor** and a NSAID
AB An oral pharmaceutical dosage form comprising an acid susceptible **proton pump inhibitor** and one or more NSAIDs in a fixed formulation, wherein the **proton pump inhibitor** is protected by an enteric coating layer. The fixed formulation is in the form of an enteric coating layered tablet,. . .
SUMM . . . of gastrointestinal disorders associated with the use of Non Steroidal Antiinflanmmatory Drugs (NSAIDs). The present preparations comprise an acid susceptible **proton pump inhibitor** in combination with one or more NSAID(s) in a new fixed unit dosage form, especially a tableted dosage form. Furthermore,. . .
SUMM Omeprazole being a well known **proton pump inhibitor** has been shown to be able to prevent gastric and duodenal erosions in healthy volunteers during treatment with acetyl salicylic. . .
SUMM . . . specific arrangement is taken to avoid degradation if the gastric acid inhibitor is an acid susceptible compound, such as a **proton pump inhibitor**.
SUMM In proposed therapies comprising NSAID(s) and an acid susceptible **proton pump inhibitor** the different active substances are administered separately. It is well known that patient compliance is a main factor in receiving. . .
SUMM . . . mentioned above. In respect of the stability properties, it is obvious that the one of the active substances being a **proton pump inhibitor** must be protected from contact with acidic gastric juice by an enteric coating layer. There are different enteric coating layered. . .
SUMM . . . Preparation of a multiple unit tableted dosage form arises specific problems when enteric coating layered pellets containing the acid susceptible **proton pump inhibitor** are compressed into tablets. If the enteric coating layer does not withstand the compression of the pellets into a tablet,. . .
SUMM The present invention provides oral, fixed unit dosage forms, i.e. multiple unit tableted dosage forms, enteric coating layered tablets, **multilayered** tablets or capsules filled with more than one pharmaceutically active compound. The active compounds are preferably an

acid susceptible **proton pump inhibitor** in combination with one or more NSAIDs and wherein at least the **proton pump inhibitor** is protected by an enteric coated layer. These new dosage forms will simplify the regimen and improve the patient compliance.

DRWD FIG. 1 illustrates a cross-section of a multiple unit tableted dosage form comprising an acid susceptible **proton pump inhibitor** in the form of enteric coating layered pellets (1) in admixture with a fast disintegrating granulate comprising a NSAID (2).. . .

DRWD FIG. 2 illustrates a cross-section of a multiple unit tableted dosage form comprising an acid susceptible **proton pump inhibitor** in the form of enteric coating layered pellets (1) and a NSAID in the form of cyclodextrin complex (3) included. . .

DRWD FIG. 3 illustrates a cross-section of a tablet with two separate layers, one layer comprises an acid susceptible **proton pump inhibitor** in the form of enteric coating layered pellets (1) in admixture with excipients (5) and the other layer comprises a. . .

DRWD FIG. 4 illustrates a cross-section of a multiple unit tableted dosage form comprising an acid susceptible **proton pump inhibitor** in the form of enteric coating layered pellets (1) and a NSAID in the form of enteric coating layered pellets. . .

DRWD FIG. 5 illustrates a cross-section of an enteric coating layered tablet comprising an acid susceptible **proton pump inhibitor** (8) in admixture with one or more NSAID(s) (9) and excipients (5). The tablet is covered by an enteric coating. . .

DRWD FIG. 6 illustrates a tablet comprising an acid susceptible **proton pump inhibitor** in the form of enteric coating layered pellets (1) in admixture with a fast disintegrating granulate (4) in a tablet. . .

DETD . . . the invention is to provide an oral, multiple unit tableted dosage form comprising an anti-ulcer drug, preferably an acid susceptible **proton pump inhibitor** in the form of individually enteric coating layered units, together with one or more NSAIDs and tablet excipients compressed into a tablet The enteric coating layer(s) covering the individual units of the acid susceptible **proton pump inhibitor** has properties such that the compression of the units into a tablet does not significantly affect the acid resistance of. . .

DETD Alternatively, the prepared tablet has separate layers, one layer that comprises the acid susceptible **proton pump inhibitor** in the form of compressed enteric coated layered units and another layer that comprises the NSAID(s).

DETD Further alternatives are exemplified as multiple unit dosage forms wherein the **proton pump inhibitor** is in the form of individually enteric coating layered units and the NSAID(s) in the form of a) a complex. . . preparation with extended release of the NSAID(s), see FIG. 3. A further alternative is a multiple dosage form with the **proton pump inhibitor** in the form of individually enteric coating layered units compressed into a tablet and thereupon a separate layer of the. . .

DETD . . . alternative, the different active substances are dry mixed and filled into a capsule. In the latter preparation the acid susceptible **proton pump inhibitor** is in the form of enteric coating layered units and the NSAID(s) is/are in the form of granules or alternatively. . .

DETD The anti-ulcer drug is preferably an acid susceptible **proton pump inhibitor**. Such proton pump inhibitors are for example compounds of the general formula I ##STR1##

DETD A wide variety of NSAIDs may be used in combination with a suitable **proton pump inhibitor** and optional pharmaceutically acceptable excipients in the fixed unit dosage form according to the present invention. Such NSAIDs include for. . .

DETD The preferred multiple unit tableted dosage form comprising a **proton pump inhibitor** (in the form of a racemat, an alkaline salt or one of its single enantiomers) and one or more NSAIDs, is characterized in the following way. Individually enteric coating layered units (small beads, granules or pellets) containing the **proton pump inhibitor** and optionally containing alkaline reacting substances, are mixed with the NSAID(s) and conventional tablet excipients. Preferably, the NSAID(s) and tablet. . . "individual units" is meant small beads, granules or pellets, in the following referred to as pellets of the acid susceptible **proton pump inhibitor**.

DETD . . . tableted dosage form must not significantly affect the acid resistance of the enteric coating layered pellets comprising the acid susceptible **proton pump inhibitor**. In other words the mechanical

properties, such as the flexibility and hardness as well as the thickness of the enteric. . .

DETD The acid resistance is defined as the amount of **proton pump inhibitor** in the tablets or pellets after being exposed to simulated gastric fluid USP, or to 0,1 M HCl (aq) relative. . . pellets to the medium. After two hours the enteric coating layered pellets are removed and analyzed for content of the **proton pump inhibitor** using High Performance Liquid Chromatography (HPLC).

DETD . . . core material for the individually enteric coating layered pellets can be constituted according to different principles. Seeds layered with the **proton pump inhibitor**, optionally mixed with alkaline substances, can be used as the core material for the further processing.

DETD The seeds which are to be layered with the **proton pump inhibitor** can be water insoluble seeds comprising different oxides, celluloses, organic polymers and other materials, alone or in mixtures or water-soluble. . . seeds comprising different inorganic salts, sugars, non-pareils and other materials, alone or in mixtures. Further, the seeds may comprise the **proton pump inhibitor** in the form of crystals, agglomerates, compacts etc. The size of the seeds is not essential for the present invention but may vary between approximately 0.1 and 2 mm. The seeds layered with the **proton pump inhibitor** are produced either by powder or solution/suspension layering using for instance granulation or spray coating layering equipment.

DETD Before the seeds are layered, the **proton pump inhibitor** may be mixed with further components. Such components can be binders, surfactants fillers, disintegrating agents, alkaline additives or other and/or. . .

DETD Alternatively, the **proton pump inhibitor** optionally mixed with alkaline substances and further mixed with suitable constituents can be formulated into a core material. Said core. . . and preferably between 0.1 and 2 mm. The manufactured core material can further be layered with additional ingredients comprising the **proton pump inhibitor** and/or be used for further processing.

DETD The **proton pump inhibitor** is mixed with pharmaceutical constituents to obtain preferred handling and processing properties and a suitable concentration of the **proton pump inhibitor** in the final preparation. Pharmaceutical constituents such as fillers, binders, lubricants, disintegrating agents, surfactants and other pharmaceutically acceptable additives may. . .

DETD Further, the **proton pump inhibitor** may also be mixed with an alkaline, pharmaceutically acceptable substance (or substances). Such substances can be chosen among, but are. . . carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminium hydroxide/sodium bicarbonate coprecipitate; substances normally used in **antacid** preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $Al_{203}.6MgO.CO_2.12H_{20}$, $(Mg_{6Al2}(OH)_{16CO_3}.4H_{20})$, $MgO.Al_{203}.2SiO_2.nH_{20}$ or similar.

. .

DETD . . . separate(s) the core material from the outer layers being enteric coating layer(s). This/these separating layer(s) protecting the core material of **proton pump inhibitor** should be water soluble or rapidly disintegrating in water.

DETD . . . layer(s) can be further strengthened by introducing into the layer(s) substances chosen from a group of compounds usually used in **antacid** formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds. . .

DETD . . . and to decrease diffusion of acidic gastric juices into the acid susceptible material. To protect the acid susceptible substance, the **proton pump inhibitor**, and to obtain an acceptable acid resistance of the dosage form according to the invention, the enteric coating layer(s) constitutes. . .

DETD . . . layer described above may also be used for an enteric coating layer of conventional tablets comprising a composition of a **proton pump inhibitor** and one or more NSAIDs, optionally the prepared tablet core also is covered by one of the separating layers described.

. .

DETD The enteric coating layered pellets comprising a **proton pump inhibitor** are mixed with the granules comprising NSAID(s) and tablet excipients. The mixture is compressed into a multiple unit tableted

dosage. . .

DETD Alternatively, the NSAID(s) may be dry mixed with the enteric coating layered pellets comprising the **proton pump inhibitor** optionally together with inactive excipients and compressed into tablets (direct compression), or the different active substances may be formulated in. . .

DETD Further, both the NSAID(s) and the **proton pump inhibitor** in the form of enteric coating layered pellets may be mixed with inactive tablet excipients and compressed into a tablet. . .

DETD As a further alternative a multiple unit tableted dosage form comprising the **proton pump inhibitor** is spray coating layered by a suspension or solution comprising the NSAID(s). The prepared tablet is thereafter covered by a. . .

DETD . . . preferably less than 60%. By increasing the amount of the granules comprising the NSAID(s) the fraction of enteric coating layered **proton pump inhibitor** pellets in the multiple unit dosage form may be reduced. By choosing small enteric coating layered pellets in the formulation. . .

DETD . . . unit tablet formulation consists of enteric coating layered pellets containing one active substance in the form of an acid susceptible **proton pump inhibitor**, optionally mixed with alkaline reacting compound(s), compressed into tablet together with granules containing NSAID(s) and optionally tablet excipients. The addition of an alkaline reacting material to the **proton pump inhibitor** is not necessary, in any sense but such a substance may further enhance the stability of the **proton pump inhibitor** or some of the alkaline reacting compounds may react in situ with the enteric coating material to form a separating. . . media such as, for instance the liquids present in the proximal part of the small intestine, where dissolution of the **proton pump inhibitor** is desired. The NSAID(s) may be released in the stomach. The enteric coating layered pellets may further be covered with. . .

DETD . . . form represents a further aspect of the invention. After formulation of the pellets by spray coating or layering of the **proton pump inhibitor** onto seeds, or by extrusion/spheronization or granulation, e.g. rotor granulation of homogeneous pellets, the pellets are first optionally covered with. . .

DETD . . . layer. The NSAID(s) may also be incorporated in a coating layer applied onto a multiple unit dosage form comprising the **proton pump inhibitor**, or the NSAID(s) and **proton pump inhibitor** in the form of enteric coating layered pellets are mixed with inactive tablet excipients and compressed into a multiple unit. . .

DETD . . . comprising the NSAID(s) may be in the form of a control release preparation. As a further alternative, the acid susceptible **proton pump inhibitor** in the form of enteric coating layered pellets may be filled in a capsule together with the NSAID(s) in the. . .

DETD . . . of the patients, the mode of administration and disease. In general each dosage form will comprise 0,1-200 mg of the **proton pump inhibitor** and 0,1-1000 mg of the NSAID(s). Preferably, each dosage form will comprise 10-80 mg of the **proton pump inhibitor** and 10-800 mg of the NSAID(s), and more preferably 10-40 mg of **proton pump inhibitor** and 10-500 mg of the NSAID(s), respectively. Especially preferred combinations comprise for instance 10 mg omeprazole together with 50 mg. . .

DETD **Two-layered** tablet dosage form with fast disintegrating part having 20 mg of lansoprazole in the form of enteric coated pellets comprised. . .

DETD . . . MCC and 18.2 mg of crosslinked polyvinylpyrrolidone per tablet, on top. These materials were then compressed together to give the **two-layered** tablets on a Diaf s tableting machine equipped with 9×20 mm punches. Tablet hardness tested with a Schleuniger apparatus over. . .

DETD The enteric coating layered pellets comprising a **proton pump inhibitor** may also be prepared as described in the following examples.

CLM What is claimed is:

1. A capsule formulation comprising an acid susceptible **proton pump inhibitor**, one or more Non Steroidal Antiinflammatory Drugs (NSAID(s)), an enteric coating layer to protect the **proton pump inhibitor** and, optionally, pharmaceutically acceptable excipients.

2. The capsule formulation according to claim 1, wherein the **proton pump inhibitor** is in the form of pellets covered with an enteric

coating layer.

4. The capsule formulation according to claim 1, wherein the dosage form comprises the **proton pump inhibitor** and one NSAID.

5. The capsule formulation according to claim 1, wherein the **proton pump inhibitor** is omeprazole, an alkaline salt of omeprazole, a single enantiomer of omeprazole or an alkaline salt of the single enantiomer.

. . .

6. The capsule formulation according to claim 5, wherein the **proton pump inhibitor** is S-omeprazole magnesium salt.

7. The capsule formulation according to claim 1, wherein the **proton pump inhibitor** is lansoprazole, a pharmaceutically acceptable salt of lansoprazole, a single enantiomer of lansoprazole or a pharmaceutically acceptable salt of the. . .

8. The capsule formulation according to claim 1, wherein the **proton pump inhibitor** is pantoprazole, a pharmaceutically acceptable salt of pantoprazole, a single enantiomer of pantoprazole or a pharmaceutically acceptable salt of the. . .

11. The capsule formulation according to claim 1, wherein the amount of the **proton pump inhibitor** is in the range of 10-80 mg and the amount of NSAID(s) is in the range of 10-800 mg.

12. The capsule formulation according to claim 1, wherein the amount of the **proton pump inhibitor** is in the range of 10-40 mg and the amount of NSAID(s) is in the range of 10-500 mg.

17. The capsule formulation according to claim 1, wherein the **proton pump inhibitor** is in the form of pellets covered with an enteric coating layer, and wherein the NSAID(s), is in the form. . .

18. The capsule formulation according to claim 1, wherein the **proton pump inhibitor** is in the form of pellets covered with an enteric coating layer, and wherein the NSAID(s) is in the form. . .

19. A process for the manufacture of a capsule formulation comprising a **proton pump inhibitor** and one or more Non Steroidal Antiinflammatory Drugs (NSAID(s)), wherein the process comprises the steps: (a) preparing the **proton pump inhibitor** in the form of enteric coating layered pellets, and (b) filling a capsule with the pellets, the NSAID(s) selected from. . .

L20 ANSWER 31 OF 31 USPAT2 on STN
Full Text
AN 2002:85601 USPAT2
TI Substituted benzimidazole dosage forms and method of using same
IN Phillips, Jeffrey O., Ashland, MO, United States
PI US 6645988 B2 20031111
AB . . . There is provided a liquid or solid pharmaceutical dosage form that is not enteric coated or delayed released containing a **proton pump inhibitor** and a Primary Essential Buffer. When the dosage form is placed in a liquid phase the Primary Essential Buffer maintains the pH of the environment at a value greater than the pKa of the **proton pump inhibitor** for a time sufficient to substantially avoid acid degradation of the **proton pump inhibitor** in the environment. Also provided is a method for treating acid-related gastrointestinal disorders by administering a solid pharmaceutical dosage form;. . .
SUMM . . . as critically ill patients, children, the elderly, and patients suffering from dysphagia. Therefore, it would be desirable to formulate a **proton pump inhibitor** solution or suspension which can be enterally delivered to a patient thereby providing the benefits of the **proton pump inhibitor** without the drawbacks of the current enteric-coated solid dosage forms.
SUMM Omeprazole, the first **proton pump inhibitor** introduced into use, has been formulated in many different embodiments such as in a mixture of polyethylene glycols, adeps solidus. . .
SUMM . . . the diseased or affected areas, namely the stomach and upper gastrointestinal tract, nor does this omeprazole formulation provide the immediate **antacid** effect of the present formulation.
SUMM . . . tablets or pellets, nor does it teach a convenient form which can be used to make an omeprazole or other **proton pump inhibitor** solution or suspension.

SUMM Fifth, excessive **antacid** intake (such as sodium bicarbonate) can result in drug interactions that produce serious adverse effects. For example, by altering gastric. . .

SUMM . . . a year while still maintaining 99% of its initial potency. It would be desirable to have an omeprazole or other **proton pump inhibitor** solution or suspension that could be stored at room temperature or in a refrigerator for periods of time which exceed. . .

SUMM It would, therefore, be desirable to have a **proton pump inhibitor** formulation, which provides a cost-effective means for the treatment of the aforementioned conditions without the adverse effect profile of H_2 receptor antagonists, antacids, and sucralfate. Further, it would be desirable to have a **proton pump inhibitor** formulation which is convenient to prepare and administer to patients unable to ingest solid dosage forms such as tablets or. . . the liquid formulation not clog indwelling tubes, such as nasogastric tubes or other similar tubes, and which acts as an **antacid** immediately upon delivery.

SUMM The foregoing advantages and objects are accomplished by the present invention. The present invention provides an oral solution/suspension comprising a **proton pump inhibitor** and at least one buffering agent. The **PPI** can be any substituted benzimidazole compound having H+,K+-ATPase inhibiting activity and being unstable to acid. The inventive composition can alternatively. . . granules. Such dosage forms are advantageously devoid of any enteric coating or delayed or sustained-release delivery mechanisms, and comprise a **PPI** and at least one buffering agent to protect the **PPI** against acid degradation. Both the liquid and dry dosage forms can further include anti-foaming agents, parietal cell activators and flavoring. . .

SUMM In another embodiment, oral dosage forms are disclosed comprising a combination of enteric-coated or delayed-released **PPI** with an **antacid**(s). Such forms may optionally comprise non-enteric-coated **PPI**.

SUMM Additionally, the present invention relates to a method for enhancing the pharmacological activity of an intravenously administered **proton pump inhibitor** in which at least one parietal cell activator is orally administered to the patient before, during and/or after the intravenous administration of the **proton pump inhibitor**.

DETD In general, the present invention relates to a pharmaceutical composition comprising a **proton pump inhibitor** and a buffering agent with or without one or more parietal cell activators, and which is not enteric coated, sustained. . .

DETD For the purposes of this application, the term "**proton pump inhibitor**" (or "PPI") shall mean any substituted benzimidazole possessing pharmacological activity as an inhibitor of H+,K+-ATPase, including, but not limited to, omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, pariprazole, and leminoprazole. The definition of "PPI" also means that the active agents of the present invention may be administered, if desired, in the form of salts,. . .

DETD After absorption of the **PPI** (or administration intravenously) the drug is delivered via the bloodstream to various tissues and cells of the body including the parietal cells. Not intending to be bound by any one theory, research suggests that when **PPI** is in the form of a weak base and is non-ionized, it freely passes through physiologic membranes, including the cellular membranes of the parietal cell. It is believed that the non-ionized **PPI** moves into the acid-secreting portion of the parietal cell, the secretory canaliculus. Once in the acidic milieu of the secretory canaliculus, the **PPI** is apparently protonated (ionized) and converted to the active form of the drug. Generally, ionized proton pump inhibitors are membrane. . . with cysteine residues in the alpha subunit of the proton pump. Such active forms are included within the definition of "PPI" herein.

DETD The inventive pharmaceutical composition comprising a **proton pump inhibitor** such as omeprazole, lansoprazole or other **proton pump inhibitor** and derivatives thereof can be used for the treatment or prevention of gastrointestinal conditions including, but not limited to, active. . .

DETD The **proton pump inhibitor** is administered and dosed in accordance with good medical practice, taking into account the clinical condition of the individual patient,. . . factors known to medical practitioners. The term "effective amount" means, consistent with considerations known in the art, the amount of **PPI** or other agent effective to achieve a pharmacologic effect or therapeutic improvement

without undue adverse side effects, including but not. . .

DETD . . . in the GI tract. In order to avoid the critical disadvantages associated with administering large amounts of sodium bicarbonate, the **PPI** solution of the present invention is administered in a single dose which does not require any further administration of bicarbonate, or other buffer following the administration of the **PPI** solution, nor does it require a large amount of bicarbonate or buffer in total. That is, unlike the prior art **PPI** solutions and administration protocols outlined above, the formulation of the present invention is given in a single dose, which does not require administration of bicarbonate either before or after administration of the **PPI**. The present invention eliminates the need to pre- or post-dose with additional volumes of water and sodium bicarbonate. The amount. . .

DETD . . . pharmaceutical composition of the present invention is prepared by mixing omeprazole enteric-coated granules (Prilosec® AstraZeneca), or omeprazole base, or other **proton pump inhibitor** or derivatives thereof with a solution including at least one buffering agent (with or without a parietal cell activator, as discussed below). In one embodiment, omeprazole or other **proton pump inhibitor**, which can be obtained from powder, capsules, and tablets or obtained from the solution for parenteral administration, is mixed with a sodium bicarbonate solution to achieve a desired final omeprazole (or other **PPI**) concentration. As an example, the concentration of omeprazole in the solution can range from approximately 0.4 mg/ml to approximately 10.0. . .

DETD . . . weak base or strong base (and mixtures thereof) that, when formulated or delivered with (e.g., before, during and/or after) the **PPI**, functions to substantially prevent or inhibit the acid degradation of the **PPI** by gastric acid sufficient to preserve the bioavailability of the **PPI** administered. The buffering agent is administered in an amount sufficient to substantially achieve the above functionality. Therefore, the buffering agent. . .

DETD The inventive solutions and other dosage forms of the present invention have pharmacokinetic advantages over standard enteric-coated and time-released PPI dosage forms, including: (a) more rapid drug absorbance time (about 10 to 60 minutes) following administration for the **PPI** solution or dry form versus about 1 to 3 hours following administration for the enteric-coated pellets; (b) the buffer solution protects the PPI from acid degradation prior to absorption; (c) the buffer acts as an **antacid** while the **PPI** is being absorbed for rapid **antacid** relief; and (d) the solutions can be administered through an existing indwelling tube without clogging, for example, nasogastric or other. . .

DETD . . . agents such as methyl cellulose are desirable to use in order to reduce the settling of the omeprazole or other **PPI** or derivatives thereof from the suspension.

DETD The present invention further includes a pharmaceutical composition comprising omeprazole or other **proton pump inhibitor** and derivatives thereof and at least one buffering agent in a form convenient for storage, whereby when the composition is. . .

DETD . . . solution maintains greater than 90% of its potency for 12 months. By providing a pharmaceutical composition including omeprazole or other **PPI** with buffer in a solid form, which can be later dissolved or suspended in a prescribed amount of aqueous solution. . .

DETD . . . present pharmaceutical tablets or other solid dosage forms disintegrate rapidly in aqueous media and form an aqueous solution of the **PPI** and buffering agent with minimal shaking or agitation. Such tablets utilize commonly available materials and achieve these and other desirable objectives. The tablets or other solid dosage forms of this invention provide for precise dosing of a **PPI** that may be of low solubility in water. They may be particularly useful for medicating children and the elderly and. . .

DETD . . . after they are placed in water, and are readily dispersible to form a suspension containing a precise dosage of the **PPI**. The suspension tablets of this invention comprise, in combination, a therapeutic amount of a **PPI**, a buffering agent, and a disintegrant. More particularly, the suspension tablets comprise about 20 mg omeprazole and about 4-30 mEq. . .

DETD . . . magnesium silicate, magnesium aluminate, aluminum hydroxide or aluminum magnesium hydroxide. A particular alkali earth metal salt useful for making an **antacid** tablet is calcium carbonate.

DETD . . . may contain many different variations of the above components.

For example, if the tablets or powder are compounded to contain **PPI** and buffering agent, the diluent may be water, sodium bicarbonate, or other compatible diluent, and the dose cup can be. . .

DETD . . . chocolate, calcium and sodium bicarbonate and other alkaline substances, stimulate the parietal cells and enhance the pharmacologic activity of the **PPI** administered. For the purposes of this application, "parietal cell activator" or "activator" shall mean any compound or mixture of compounds. . .

DETD . . . amount of about 5 mg to 2.5 g per 20 mg dose of omeprazole (or equivalent pharmacologic dose of other **PPI**). The dose of activator administered to a mammal, particularly a human, in the context of the present invention should be sufficient to effect a therapeutic response (i.e., enhanced effect of **PPI**) over a reasonable time frame. The dose will be determined by the strength of the particular compositions employed and the. . .

DETD The approximate effective ranges for various parietal cell activators per 20 mg dose of omeprazole (or equivalent dose of other **PPI**) are:

DETD . . . further alternative, sodium bicarbonate powder (about 975 mg per 20 mg dose of omeprazole (or an equipotent amount of other **PPI**) is compounded directly into the tablet. Such tablets are then dissolved in water or sodium bicarbonate 8.4%, or swallowed whole. . .

DETD

B1. 10 mg Tablet Formula.
Omeprazole 10 mg (or lansoprazole or pantoprazole or other **PPI** in an equipotent amount)
Calcium lactate 175 mg
Calcium glycerophosphate 175 mg
Sodium bicarbonate 250 mg
Aspartame calcium (phenylalanine) 0.5 mg
Colloidal silicon dioxide 12. . . starch 15 mg
Croscarmellose sodium 12 mg
Dextrose 10 mg
Peppermint 3 mg
Maltodextrin 3 mg
Mannitol 3 mg
Pregelatinized starch 3 mg
B2. 10 mg Tablet Formula.
PPI: one of the following:
Omeprazole 10 mg
Lansoprazole 15 mg
Pantoprazole sodium 20 mg
Rabeprazole sodium 10 mg
Other **PPI** in an equipotent amount
Calcium lactate 375 mg
Calcium glycerophosphate 375 mg
Aspartame calcium (phenylalanine) 0.5 mg
Colloidal silicon dioxide 12 mg
Corn starch 15 mg
Croscarmellose sodium 12 mg
Dextrose 10 mg
Peppermint 3 mg
Maltodextrin 20 mg
Mannitol 30 mg
Pregelatinized starch 30 mg
B3. 10 mg Tablet Formula.
PPI: one of the following:
Omeprazole 10 mg
Lansoprazole 15 mg
Pantoprazole sodium 20 mg
Rabeprazole sodium 10 mg
Other **PPI** in an equipotent amount
Sodium bicarbonate 750 mg
Aspartame sodium (phenylalanine) 0.5 mg
Colloidal silicon dioxide 12 mg
Corn starch 15 mg
Croscarmellose sodium 12. . . mg
Maltodextrin 20 mg
Mannitol 30 mg
Pregelatinized starch 30 mg
C1. 20 mg Tablet Formula.
Omeprazole 20 mg (or lansoprazole or pantoprazole or

other **PPI** in an equipotent amount)
Calcium lactate 175 mg
Calcium glycerophosphate 175 mg
Sodium bicarbonate 250 mg
Aspartame calcium (phenylalanine) 0.5 mg
Colloidal silicon dioxide 12. . . sodium 12 mg
Dextrose 10 mg
Calcium hydroxide 10 mg
Peppermint 3 mg
Maltodextrin 3 mg
Mannitol 3 mg
Pregelatinized starch 3 mg
C2. 20 mg Tablet Formula.
PPI: One of the following:
Omeprazole 20 mg
Lansoprazole 30 mg
Pantoprazole 40 mg
Other **PPI** in an equipotent amount
Calcium lactate 375 mg
Calcium glycerophosphate 375 mg
Aspartame calcium (phenylalanine) 0.5 mg
Colloidal silicon dioxide 12 mg
Corn starch 15 mg
Croscarmellose sodium 12 mg
Dextrose 10 mg
Peppermint 3 mg
Maltodextrin 20 mg
Mannitol 30 mg
Pregelatinized starch 30 mg
C3. 20 mg Tablet Formula.
PPI: One of the following:
Omeprazole 20 mg
Lansoprazole 30 mg
Pantoprazole 40 mg
Other **PPI** in an equipotent amount
Sodium bicarbonate 750 mg
Aspartame sodium (phenylalanine) 0.5 mg
Colloidal silicon dioxide 12 mg
Corn starch 15 mg
Croscarmellose sodium 12. . . mg
Maltodextrin 20 mg
Mannitol 30 mg
Pregelatinized starch 30 mg
D1. Tablet for Rapid Dissolution.
Omeprazole 20 mg (or lansoprazole or pantoprazole or other **PPI** in an equipotent amount)
Calcium lactate 175 mg
Calcium glycerophosphate 175 mg
Sodium bicarbonate 500 mg
Calcium hydroxide 50 mg
Croscarmellose sodium 12 mg
D2. Tablet for Rapid Dissolution.
PPI: One of the following:
Omeprazole 20 mg
Lansoprazole 30 mg
Pantoprazole 40 mg
Rabeprazole sodium 20 mg
Esomeprazole magnesium 20 mg
Other **PPI** in an equipotent amount
Calcium lactate 300 mg
Calcium glycerophosphate 300 mg
Calcium hydroxide 50 mg
Croscarmellose sodium 12 mg
D3. Tablet for Rapid Dissolution.
PPI: One of the following:
Omeprazole 20 mg
Lansoprazole 30 mg
Pantoprazole 40 mg
Rabeprazole sodium 20 mg
Esomeprazole magnesium 20 mg
Other **PPI** in an equipotent amount
Sodium bicarbonate 700 mg

Trisodium phosphate dodecahydrate 100 mg
Croscarmellose sodium 12 mg
E1. Powder for Reconstitution
for Oral Use (or per ng tube).
Omeprazole 20 mg (or lansoprazole or pantoprazole or
other **PPI** in an equipotent amount)
Calcium lactate 175 mg
Calcium glycerophosphate 175 mg
Sodium bicarbonate 500 mg
Calcium hydroxide 50 mg
Glycerine 200 mg
E2. Powder for Reconstitution
for Oral Use (or per ng tube).
PPI: One of the following:
Omeprazole 20 mg
Lansoprazole 30 mg
Pantoprazole 40 mg
Rabeprazole sodium 20 mg
Esomeprazole magnesium 20 mg
Other **PPI** in an equipotent amount
Calcium lactate 300 mg
Calcium glycerophosphate 300 mg
Calcium hydroxide 50 mg
Glycerine 200 mg
E3. Powder for Reconstitution
for Oral Use (or per ng tube).
PPI: One of the following:
Omeprazole 20 mg
Lansoprazole 30 mg
Pantoprazole 40 mg
Rabeprazole sodium 20 mg
Esomeprazole magnesium 20 mg
Other **PPI** in an equipotent amount
Sodium bicarbonate 850 mg
Trisodium phosphate 50 mg
F1. 10 mg Tablet Formula.
Omeprazole 10 mg (or lansoprazole or pantoprazole or
other **PPI** in an equipotent amount)
Calcium lactate 175 mg
Calcium glycerophosphate 175 mg
Sodium bicarbonate 250 mg
Polyethylene glycol 20 mg
Croscarmellose sodium 12 mg
Peppermint 3 mg
Magnesium silicate 1 mg
Magnesium stearate 1 mg
F2. 10 mg Tablet Formula.
PPI: One of the following:
Omeprazole 10 mg
Lansoprazole 15 mg
Pantoprazole sodium 20 mg
Rabeprazole sodium 10 mg
Esomeprazole magnesium 10 mg
Other **PPI** in an equipotent amount
Calcium lactate 475 mg
Calcium glycerophosphate 250 mg
Polyethylene glycol 20 mg
Croscarmellose sodium 12 mg
Peppermint 3 mg
Magnesium silicate 10 mg
Magnesium stearate 10 mg
F3. 10 mg Tablet Formula.
PPI: One of the following:
Omeprazole 10 mg
Lansoprazole 15 mg
Pantoprazole sodium 20 mg
Rabeprazole sodium 10 mg
Esomeprazole magnesium 10 mg
Other **PPI** in an equipotent amount
Sodium bicarbonate 700 mg
Polyethylene glycol 20 mg
Croscarmellose sodium 12 mg

Peppermint 3 mg
Magnesium silicate 10 mg
Magnesium stearate 10 mg
G1. 10 mg Tablet Formula.
Omeprazole 10 mg (or lansoprazole or pantoprazole or other **PPI** in an equipotent amount)
Calcium lactate 200 mg
Calcium glycerophosphate 200 mg
Sodium bicarbonate 400 mg
Croscarmellose sodium 12 mg
Pregelatinized starch 3 mg
G2. 10 mg Tablet Formula.
PPI: One of the following:
Omeprazole 10 mg
Lansoprazole 15 mg
Pantoprazole sodium 20 mg
Rabeprazole sodium 10 mg
Esomeprazole magnesium 10 mg
Other **PPI** in an equipotent amount
Calcium lactate 400 mg
Calcium glycerophosphate 400 mg
Croscarmellose sodium 12 mg
Pregelatinized starch 3 mg
G3. 10 mg Tablet Formula.
PPI: One of the following:
Omeprazole 10 mg
Lansoprazole 15 mg
Pantoprazole sodium 20 mg
Rabeprazole sodium 10 mg
Esomeprazole magnesium 10 mg
Other **PPI** in an equipotent amount
Sodium bicarboante 750 mg
Croscarmellose sodium 12 mg
Pregelatinized starch 3 mg
DETD Standard Tablet of **PPI** and Buffering Agent.
DETD **PPI** Central Core Tablet.
DETD . . . activate the effervescent agents and create the desired solution. In addition, lansoprazole 30 mg (or an equipotent dose of other **PPI**) can be substituted for omeprazole.
DETD . . . patients, 9 were excluded from the study, all based upon insufficient data about commencement, duration or outcome in treatment with **PPI** therapy. This left 24 patients with enough data to draw conclusions.
DETD Of the 24 remaining patients, 18 were males and 6 females. Ages at implementation of **PPI** therapy ranged from 2 weeks of age to 9 years old. Median age at start of therapy was 26.5 months. . . as findings in a few patients. Six patients had neither pH nor endoscopic documentation of GERD, but were tried on **PPI** therapy based on symptomatology alone.
DETD The **proton pump inhibitor** suspension used in this group of patients was Choco-Base suspension of either lansoprazole or omeprazole. The dosing was very uniform,. . .
DETD Most patients responded favorably to and tolerated the once daily dosing of Choco-Base **proton pump inhibitor** suspension. Two patients had documented adverse effects associated with the use of the **PPI** suspension. In one patient, the mother reported increased burping up and dyspepsia, which was thought to be related to treatment. . .
DETD . . . and (4) inconclusive. Of 24 patients with sufficient data for follow up, 18 showed improvement in symptomatology upon commencement of **PPI** therapy [72%]. The seven who did not respond were analyzed and grouped. Three showed no change in symptomatology and clinical. . . 8). Setting aside the cases in which therapy was stopped before conclusions could be drawn and the case in which **PPI** therapy was for purely prophylactic reasons, leaves (17/21) 81% of patients that responded to Choco-Base suspension. This means that 19% (4/21) of patients received no apparent benefit from **PPI** therapy. Of all these patients, only 4% complained of worsening symptoms and the side effects were 4% (1/21) and were. . .
DETD . . . a pro-kinetic agent and H-2 blocker therapy. Nonetheless, many patients fail this treatment protocol and become surgical candidates. In adults, **PPI** therapy is effective in 90% of those treated for gastroesophageal reflux disease. As a medical alternative to the H-2

blockers,. . . appropriate dosage should be in this group of patients. A recent review by Israel D., et al. suggests that effective **PPI** dosages should be higher than that originally reported, i.e., from 0.7 mg/kg to 2 or 3 mg/kg omeprazole. Since toxicity. . .

DETD In the ICU setting, the University of Missouri-Columbia has been using an unflavored **PPI** suspension given once daily per various tubes (nasogastric, g-tube, jejunal feeding tube, duo tube, etc.) for stress ulcer prophylaxis. It. . .

DETD . . . in the adult population, but this can be attributed to the refractory nature of their illness, most having failed prior non-**PPI** treatment. The population in this study is not indicative of general practice populations.

DETD **PPI** therapy is a beneficial therapeutic option in the treatment of reflux related symptoms in the pediatric population. Its once daily. . .

DETD In all four of the above formulations, lansoprazole or other **PPI** can be substituted for omeprazole in equipotent amounts. For example, 300 mg of lansoprazole may be substituted for the 200. . .

DETD . . . proton pump and effectively block activated proton pumps (primarily those inserted into the secretory canalicular membrane). By further administering the **proton pump inhibitor** with one of these activators or enhancers, there is a synchronization of activation of the proton pump with the absorption and subsequent parietal cell concentrations of the **proton pump inhibitor**. As illustrated in FIG. 4, this combination produced a much longer pharmacologic effect than when the **proton pump inhibitor** was administered alone.

DETD Combination Tablet Delivering Bolus And Time-Released Doses of **PPI**

DETD 1. Currently taking $H_{2\text{-receptor}}$ antagonist, **antacid**, or sucralfate.

DETD 2. Recent (within 7 days) therapy with lansoprazole, omeprazole, or other **proton pump inhibitor**.

DETD Intraveneous **PPI** in Combination With Oral Parietal Cell Activator

DETD . . . can be administered either within about 5 minutes before, during or within about 5 minutes after the IV dose of **PPI**.

DETD Applicant expects that these studies will demonstrate that significantly less IV **PPI** is required to achieve therapeutic effect when it is given in combination with an oral parietal cell activator.

DETD Additionally, administration kits of IV **PPI** and oral parietal cell activator can be packaged in many various forms for ease of administration and to optimize packing. . .

DETD VI. **PPI** Compositions and Method for Optimizing the Buffer to be Administered in Combination With a **PPI**

DETD . . . drug. Acid labile PPIs, for example, can be formulated or coadministered with one or more buffers sufficient to protect the **PPI** in any environment, with the ultimate goal being to deliver a **PPI** to the stomach (or other environment) either via a liquid, a powder or solid dosage form that produces an immediate release of active drug to the site of delivery such that the **PPI** is quickly available for absorption. Accordingly, Applicant has found that certain amounts of buffers coadministered or mixed with certain PPIs prevent acid degradation of the **PPI** when the buffers produce a pH in the stomach or other site of environment that is equal to the pKa of the **PPI** plus an amount sufficient to protect the **PPI** from acids and provide undegraded and bioactive PPI to the blood upon administration (e.g., a final pH of pKa of **PPI**+0.7 log value will reduce the degradation to about 10%). Such buffers should interact with hydrogen ion at rates that exceed the interaction of hydrogen ion with the **PPI**. Thus, the solubilities of the buffers and PPIs are important considerations because solubility is a key determinant of the rate. . .

DETD Typically, a PPI formulation of the present invention comprises two primary components: a **PPI** and an Essential Buffer. An Essential Buffer may include a buffer or combination of buffers that interact with HCl (or other acids in the environment of interest) faster than the **PPI** interacts with the same acids. When placed in a liquid phase (usually in water), the Essential Buffer produces and maintains a pH of at least the pKa of the **PPI**. In one embodiment, by raising the pH of the environment to the same of the pKa of the **PPI** plus about 0.7 log value (or greater), the expected degradation (ionization) can be reduced from about 50% to about 10%.. . . pH" is the lowest pH of the environment of interest needed to minimize or eliminate the acid-induced degradation of the **PPI**. The buffering agent(s) employed may raise the pH of the environment to the Essential pH such that 30%, 40% or 50% of the **PPI** is undegraded, or be present in an amount sufficient to substantially

protect (i.e., greater than 50% stability) the **PPI**.

DETD In another embodiment, the Essential pH is the pKa of the **PPI**. In a further embodiment, the Essential pH is the sum of the pKa of the **PPI** plus log 0.7. A log value of about 0.7 is added to the pKa, which represents a decrease of about 5.01187% in stability of the **PPI** from the pKa plus 1 log value, thus resulting in a stability of approximately 90%, a value widely accepted as. . .

DETD . . . (Essential Buffer Capacity ("EBC")) to maintain the elevated pH of the environment (usually gastric) throughout the dwell time that the **PPI** is passed from the environment and into the blood.

DETD . . . the value that leads to tissue irritation or damage and above a lower limit for the Essential pH of the **PPI**. Secondary Essential Buffers are not required in every formulation but can be combined with Primary Essential Buffers to produce a. . .

DETD . . . the type and dose of buffer to protect acid labile substituted benzimidazole PPIs (and other drugs) is useful for efficacious **PPI** delivery to and action upon parietal cell proton pumps, particularly when the **PPI** is administered as an immediate release product designed to disintegrate in the stomach rather than a traditional delayed-release product designed. . . the buffer(s) to be used, as well as calculations to determine Essential pH, buffering capacity, and volume measurements for individual **PPI** doses based on their respective solubilities and pKa's. Such inventive methods are applicable for determining the type and amount of buffer(s) necessary to protect the **PPI** in an array of environments (e.g., mouth, esophagus, stomach, duodenum, jejunum, rectal vault, nasogastric tube, or a powder, tablet, capsule,. . .

DETD The Essential Buffering Capacity ("EBC") is the capacity of a **PPI**/buffer formulation to resist degradation from its environment. The buffering capacity of a **PPI**/buffer formulation is primarily derived from components of the formulation that possess the ability to combine with acids (H+ ions) from the environment. The EBC contributes to both acid neutralization (**antacid** effect) and to maintaining an environmental pH>pKa+0.7 to protect PPIs from acid degradation throughout the dwell time. The Primary Essential. . . (or other environment) at a somewhat constant level within a desired range for a period of time so that the **PPI** can be absorbed from the gastric or other environment. Accordingly, the Essential Buffer is generally more rapid in its complexation with HCl (or other acid) than the **PPI** administered so that the Essential Buffer is capable of protecting the **PPI**.

DETD Secondary Essential Buffers do not play an important role in protecting the **PPI** from early acid-induced degradation. Because they do not work as rapidly, they do not play a major role in **PPI** protection through the dwell time. Other buffers ("Non-Essential Buffers") can be added to the Primary and/or Secondary Essential Buffers to provide a latent **antacid** effect that extends beyond the **antacid** effect of Essential Buffers.

DETD . . . feeds or other sources. In general, the higher the pH of the gastric environment, the greater the stability of the **PPI**, and thus the more time it has to undergo absorption into the blood and reach and act upon the proton. . .

DETD . . . pH" is the lowest pH of the environment of interest needed to minimize or eliminate the acid-induced degradation of the **PPI** during the dwell time in the environment. It is generally expressed herein as pH range. Such pH is the pH of the environment in which the **PPI**/buffer formulation resides. For example, the environment may be a storage container or the stomach. The environment presents a set of conditions to the **PPI**/buffer, such as temperature, pH, and the presence or absence of water. The dwell time is the time that the **PPI** dwells in a specific environment, i.e., the GI tract prior to its passage into a different environment, i.e. the bloodstream.. . . container of dry, powdered formulation. As used herein, "Resultant pH" is the pH that is the result of adding a **PPI**/buffer formulation to an environment of interest. "Formulation pH" is the pH of the **PPI**/buffer formulation when it is in liquid form.

DETD A **PPI** dose within its calculated pH_E range is designed to ensure sufficient **PPI** protection from acid degradation such that delivery to and action upon proton pumps occur. In one desirable embodiment, the pH_E is the sum of the pKa of a given **PPI** plus about 0.7. The pKa is defined as the pH at which 50% of a chemical is in the ionized form. When the pH of the environment equals the pKa of the **PPI**, then 50%

ionization (degradation) of the **PPI** occurs. However, by adding the factor of 0.7, this ionization is reduced to 90%.

DETD . . . is the range of pH elevation in which the lower limit is the sum of the pKa of a given **PPI**+0.7 log, and the upper limit is the pH at which elimination of acid degradation occurs without producing tissue irritation from. . .

DETD . . . buffer is an important aspect of the tissue destructive potential of an alkaline substance. Therefore, the SRF for any given **PPI** begins at the sum of the pKa of the **PPI**+0.7, and extends upwards to a pH of about 10.9.

DETD . . . SRF establishes a desirable range for the stability to the actions of H+ ion (or other acidic component) on the **PPI**/buffer formulation. Sufficient buffering capacity maintains an Essential pH as described below as "Essential Buffering Capacity."

DETD pH_E of **PPI**=pKa of **PPI**+0.7.

DETD . . . a factor of 10, any local effects within the stomach that may produce areas of lower pH that might cause **PPI** degradation. A value of +1 log value is also supported by the observation that weak bases operate most efficiently at. . .

DETD . . . However, magnesium hydroxide is not rapid in onset and care should be taken to ensure that early degradation of the **PPI** does not occur. Early degradation can be avoided by making a tablet comprising **two layers**: an inner layer of **PPI** and sodium bicarbonate, and an outer layer of magnesium hydroxide dried gel or magnesium oxide with suitable disintegrant such that. . . rapidly disintegrate in the stomach. Alternatively, the inner layer can contain the magnesium buffer and the outer layer has the **PPI** and sodium bicarbonate.

DETD . . . best suited in an outer layer of a tablet formulation with the inner layer comprising a rapid acting buffer with **PPI** (or vice versa). Alternatively, mixtures of the buffers can be employed for the outer layer. If developing a liquid formulation. . .

DETD As mentioned above, the pKa of a given **PPI** indicates inherent stability with respect to acid degradation; the lower the pKa, the more stable the **PPI**. The solubility of the **PPI** will also dictate the rate at which the **PPI** complexes with, and is degraded by, acid. These two physicochemical characteristics (pKa and solubility) of the **PPI** interact with the physicochemical characteristics of the buffer(s) (pH, buffering capacity and rate of buffering action) in the presence of acid in the environment to determine the degradation of the **PPI** over time. The less soluble a **PPI** is in water, the lower the initial degradation when placed in an acidic environment. The following Table 11 elaborates on. . .

DETD . . . overall pH of the gastric contents should be kept at least at the pKa+0.7 (i.e., 3.7) from the time the **PPI** in solution comes into contact with the gastric acid continuing throughout the dwell time. Essential Buffers for liquid formulations of. . .

DETD Another option for rabeprazole sodium (as well as any sodium salt of a **proton pump inhibitor**, which would tend to be more soluble than the base form) is to reduce the solubility of rabeprazole sodium when. . .

DETD . . . that possess high pKa's, such as rabeprazole sodium, a two-part liquid formulation can be utilized. The liquid part has the **PPI** and a high pH, but a low mEq buffering capacity. The liquid part is added to a second part that. . .

DETD . . . as a tablet, capsule or powder with a buffer(s), which disintegrate and reach solution at a rate that exceeds the **PPI** and thereby provides the Essential pH for protection of the **PPI** prior to its dissolution and interaction with the acid in the environment. Further, the tablet or capsule may be formulated to possess an outer portion of buffer and an inner portion comprising **PPI**, or a blend of **PPI** and buffer. Additional methods include formulating the buffer in a smaller particle size (e.g., micronized) and the **PPI** in a larger particle size. This results in the disintegration of the buffer component prior to disintegration of the **PPI** component. All of these methods of formulation aim to create an environment of stability for the **PPI** during the dwell time.

DETD . . . a buffer that raises the pH of the environment to greater than or equal to the pH_E of a particular **PPI** in a time sufficient to prevent significant degradation of the **PPI**. In one embodiment, the rapid acting buffer raises the pH to at least the pKa of the **PPI** plus 0.7 log value within 10 minutes.

DETD . . . the onset of pH change to equal to or greater than the

pH_E+0.7 begins before the acid-induced degradation of the **PPI** occurs, and (2) the Resultant pH at or greater than the pH_E+0.7 lasts throughout the dwell time, which is typically. . . the particle size of the buffer(s) can be reduced to enhance the dissolution rate while the particle size of the PPI can be increased. Disintegrants can be added to enhance the availability of poorly soluble buffers.

DETD . . . pH of the gastric contents (or other environment) should be kept at greater than about 4.8 from the time the **PPI** in solution comes into contact with the gastric acid continuing throughout the dwell time.

DETD . . . that contain a tablet in a tablet, the Essential Buffer complexes with the acid at a faster rate than the **PPI** it is intended to protect.

DETD When the PPI/buffer formulation is placed in the environment, the **PPI** is subject to degradation by the acid in that environment. As depicted in FIG. 9, **PPI** solubility, the pKa of the **PPI**, and the amount and concentration of acid (H+ ion) encountered in the environment are variables that can be used to determine the appropriate candidate as an Essential Buffer. Early degradation occurs when the soluble portion of the **PPI** (that portion available for immediate interaction with H+ ion) undergoes hydrolysis by H+ ion. PPIs differ in their solubility and, therefore, those that are more soluble have a potential for a higher portion of **PPI** degraded by early interaction with H+ ion. The pKa of the **PPI** and the pH of the environment of the stomach (or other site of interest) after addition of the **PPI**/buffer formulation (Resultant pH) can be used to determine the desirable Essential Buffer. By measuring the Resultant pH over time, the. . .

DETD . . . has been described in part for use in evaluating antacids by Beneyto J E, et. al., Evaluation of a New **Antacid**, Almagate, Arzneim-Forsch/Drug Res 1984; 34 (10A): 1350-4; Kerkhof N J, et al, pH-Stat Tiration of Aluminum Hydroxide Gel, J. Pharm.. . .

DETD . . . products. In addition, a sample of the test solution can be taken during the experiment to evaluate the extent of **PPI** degradation at various times. Those buffers with a suitable profile as exemplified in FIG. 9 able to maintain pH greater. . .

DETD . . . alkaline buffer, included in the dose and calculated to maintain the Essential pH range and thereby protect any substituted benzimidazole **PPI** in the gastric (or other) environment. In patients requiring continuing **PPI** administration (e.g. daily), more buffering capacity may be necessary with the first dose or first few doses than with subsequent doses because the **PPI** may encounter more acid with the initial doses. Subsequent doses will require less buffering capacity because the initial **PPI** doses will have reduced gastric acid production. The EBC could therefore be reduced in subsequent doses. The product's buffering capacity. . .

DETD Numerous references are available to assist the skilled artisan in identifying a suitable buffer companion with a **PPI** to determine the desirable characteristics stated herein. See, e.g., Holbert, et. al., A Study of **Antacid** Buffers: I. The Time Factor in Neutralization of Gastric Acidity, J. Amer. Pharm. Assn. 36: 149-51 (1947); Lin, et. al.,. . .

DETD The Desirable Volume ("DV") of a **PPI** dose may affect **PPI** delivery to and action upon parietal cell proton pumps. The DV of a dose is partly based on the EBC. For liquid formulations, a desirable volume should deliver sufficient buffer to act as an **antacid** to neutralize a substantial amount of gastric or other acids. For solid formulations such as tablets, a nominal amount of. . .

DETD . . . butterscotch, and peanut butter flavorings, used alone or in any combination. Similarly, all substances included in the formulation of any **PPI** product, including but not limited to, activators, antifoaming agents, potentiators, antioxidants, antimicrobial agents, chelators, sweeteners, thickeners, preservatives, or other additives. . .

DETD The pH_E, the EBC, and the DV of a **PPI** dose may affect **PPI** delivery to, and action upon, parietal cell proton pumps. The following calculations tailor an Essential Buffer dose for any substituted benzimidazole PPI to promote **PPI** efficacy in an oral administration.

DETD . . . order to enhance the shelf-life, higher pH values would be anticipated within the range of acceptable pH_E for a given **PPI**. As an example, rabeprazole suspensions containing various buffers were evaluated for color change because degradation of PPIs results in a. . .

DETD Similar calculations may be performed for any substituted benzimidazole

PPI and appropriate buffer(s) including, but not limited to, those exemplified above. One skilled in the art will appreciate that the. . . above steps is not critical to the invention. The above calculations may be used for formulations comprising one or more **PPI** and one or more buffers.
DETD

Formulation 5: Veterinary Formulation of Omeprazole

This formulation is particularly well suited for animals rather than humans because the dose of **PPI** is high.
EBC = 75 mEq
Essential pH (omeprazole pKa = 3.9 + 0.7 ≥ 4.6)
PPI: Omeprazole powder 500 mg (a range of 350 to 700 mg)
Primary Essential Buffer(s):
Sodium bicarbonate 5 g (59.5 mEq)
Dibasic sodium phosphate. . . Any Secondary Essential Buffer(s) may be added in higher or lower amounts to adjust pH for desired stability and additive **antacid** or buffering effect.)
DETD

Formulation 6: Veterinary Formulation of Lansoprazole

Essential pH (lansoprazole pKa = 4.1 + 0.7 ≥ 4.8)
EBC = 71.4 mEq
PPI: Lansoprazole powder 750 mg
Primary Essential Buffer(s):
Sodium bicarbonate 6 g (71.4 mEq)

(* Any Secondary Essential Buffer(s) may be added in higher or lower amounts to adjust pH for desired stability and additive **antacid** or buffering effect.)
DETD

Formulation 7: Veterinary Formulation of Lansoprazole

Essential pH (lansoprazole pKa = 4.1 + 0.7 ≥ 4.8)
EBG = 63.3 mEq
PPI:
Lansoprazole powder 750 mg
Primary Essential Buffer(s)
Sodium bicarbonate 5 g (59.5 mEq)
Secondary Essential Buffer(s):
Sodium carbonate 400 mg* (3.8 mEq)

(*Any Secondary Essential Buffer(s) may be added to adjust pH for desired stability and additive **antacid** or buffering effect.)
DETD

Formulation 8: Veterinary Formulation of Esomeprazole Magnesium

Essential pH (esomeprazole pKa = 3.9 + 0.7 ≥ 4.6)
EBC = 53.2 mEq
PPI:
Esomeprazole magnesium powder 500 mg
Primary Essential Buffer(s):
Sodium bicarbonate 5 g (47.6 mEq)
Dibasic sodium phosphate 800 mg (5.6 mEq)

(* Any Secondary Essential Buffer(s) may be added in higher or lower amounts to adjust pH for desired stability and additive **antacid** or buffering capacity.)
DETD . . . mEq)

(*Any Secondary Essential Buffer(s) may be added in higher or lower amounts to adjust pH for desired stability and additive **antacid** or buffering capacity.)
DETD

Formulation 10: Veterinary Formulation: Buffer Base Without **PPI**

EBC = 71.4 mEq
Primary Essential Buffer:
Sodium bicarbonate 6 g 71.4 mEq
Optional Secondary Essential Buffer:
Tribasic sodium. . . Any Secondary Essential Buffer may be added in higher or lower amounts to adjust pH for desired stability and additive **antacid** or buffering capacity.)
DETD . . . butterscotch flavor 100 mg, thaumatin powder 5 mg, and sucrose 30 Gm. Q.s. to 100 mL with distilled water. A **PPI** or other acid-labile drug may be added by the compounding pharmacist selected from available PPIs or acid-labile drugs from powder or enteric-coated oral solid dosage forms. Different volumes of water may be added to achieve **PPI** concentrations ranging from 0.8 to 20 mg/mL. If other acid labile drugs are employed, the range of concentrations would be. . .
DETD

Formulation 11:
Oral Buffer Complex Without **PPI** (for general use to protect acid labile drugs) Multidose Composition

Primary Essential Buffer:
Dibasic sodium phosphate or sodium 10 g (range 2. . . mg

(*Any Secondary Essential Buffer may be added in higher or lower amounts to adjust pH for desired stability and additive **antacid** or buffering capacity.)
DETD . . . maple, butter pecan and other flavorings as have been outlined previously. Different volumes of water may be added to achieve **PPI** concentrations ranging from 0.8 to 20 mg/mL.
DETD Weigh out approximately 60 g of the formulation. Add **PPI** (or other acid-labile drug) typically in the amount equivalent to 10 doses (range 1 dose to 30 doses).
DETD

Formulation 12:
Oral Buffer Complex Without **PPI** For General Use to Protect Acid Labile Drugs; Protein Free, Multi-Dose Example

Primary Essential Buffer:
Sodium bicarbonate 5 g (range 2 g. . . mg

(*Any Secondary Essential Buffer may be added in higher or lower amounts to adjust pH for desired stability and additive **antacid** or buffering capacity.)
Note that cocoa is a parietal cell activator.
DETD . . . protected from light and moisture, such as in a foil packet. Weigh out approximately 60 g of the formulation. Add **PPI** (or other acid-labile drug) typically in the amount equivalent to 10 doses (range=1 dose to 30 doses).
DETD Q.s. to 100 mL with distilled water. Different volumes of water may be added to achieve **PPI** concentrations ranging from 0.8 to 20 mg/mL.
DETD

Formulation 13:
Buffer Complex Without **PPI** For General Use to Protect Acid Labile Drugs; Protein Free, Lactose Free Multidose Example

PPI:
None (to be added later,
e.g. by compounding pharmacist)
Primary Essential Buffer(s):
Sodium bicarbonate 8 g (range 2 g. . .
DETD Weigh out approximately 60 g of the formulation. Add **PPI** (or other acid-labile drug) typically in the amount equivalent to 10 doses (range=1 dose to 30 doses). Q.s. to 100 mL with distilled water.

Different volumes of water may be added to achieve **PPI** concentrations ranging from 0.3 to 20 mg/mL.
DETD

Formulation 14:
Buffer Complex Without **PPI** For General Use to Protect Acid Labile Drugs; Protein Free, Multi-Dose Example

PPI:
None (to be added later, e.g.
by compounding pharmacist)
Primary Essential Buffer(s):
Dibasic sodium phosphate 8 g (range 2. . .
DETD Weigh out approximately 60 g of the formulation. Add **PPI** (or other acid-labile drug) typically in the amount equivalent to 10 doses (range=1 dose to 30 doses). Q.s. to 100 mL with distilled water. Different volumes of water may be added to achieve **PPI** concentrations ranging from 0.8 to 20 mg/mL.
DETD

Formulation 15:
Buffer Complex Without **PPI** For General Use to Protect Acid Labile Drugs; Protein Free, Multi-Dose Example

PPI:
None (to be added later, e.g.
by compounding pharmacist)
Primary Essential Buffer(s):
Sodium bicarbonate 8 g (range 1 g. . .
DETD . . . protected from light and moisture, such as in a foil packet. Weigh out approximately 60 g of the formulation. Add **PPI** (or other acid-labile drug) typically in the amount equivalent to 10 doses (range=1 dose to 30 doses). Q.s. to 100 mL with distilled water. Different volumes of water may be added to achieve **PPI** concentrations ranging from 0.8 to 20 mg/mL.
DETD . . . limited
to, sodium bicarbonate, sodium carbonate, dibasic sodium phosphate, and dipotassium phosphate.

Enough powder for 11 tablets is weighed out:
PPI:
Lansoprazole powder 330 mg
Primary Essential Buffer(s):
Sodium bicarbonate USP 5500 mg
Dibasic sodium phosphate 2200 mg
DETD . . . sodium bicarbonate, sodium carbonate, disodium hydrogen phosphate (dibasic sodium phosphate), and dipotassium phosphate.

Enough powder for 11 tablets is weighed out:
PPI:
Omeprazole powder USP 220 mg
Primary Essential Buffer(s):
Sodium bicarbonate USP 6500 mg
Magnesium oxide powder 1650 mg
Croscarmelose sodium. . .
DETD

Formulation 18:
One Phase Omeprazole 40 mg Tablet

Enough powder for 11 tablets is weighed out:
PPI:
Omeprazole powder USP 440 mg
Primary Essential Buffer(s):
Sodium bicarbonate USP 6500 mg
Magnesium oxide 1650 mg

Pregelatinized starch 500. . .
DETD

Formulation 19: Omeprazole Powder Formulations (single dose)

PPI:
Omeprazole powder USP 20 mg or 40 mg
(or esomeprazole magnesium).
Primary Essential Buffer(s):
Sodium bicarbonate USP powder (60 micron) 1000 mg
Magnesium oxide. . .
DETD

Formulation 23: Flavored Lansoprazole Powder (single dose)

PPI:
Lansoprazole powder USP 30 mg
Primary Essential Buffer(s):
Dibasic Sodium Phosphate USP or 1500 mg
Sodium bicarbonate USP
Sucrose. . .
DETD

Formulation 24: Unflavored Rabeprazole Powder (single dose)

PPI:
Rabeprazole sodium powder USP 20 mg
Primary Essential Buffer(s):
Disodium phosphate duohydrate USP 2000 mg
Optional Secondary Essential Buffer(s)
. . .
DETD

Formulation 25: Unflavored Rabeprazole Powder (single dose)

PPI:
Rabeprazole sodium powder USP 20 mg
Primary Essential Buffer(s):
Sodium bicarbonate USP 1200 mg
Secondary Essential Buffer(s):
Trisodium phosphate. . . hydroxide, or Tribasic potassium may be added in higher
or lower amounts to adjust pH for desired stability and additive
antacid or buffering capacity.
DETD . . . formulation is designed to enable the use of the commercially available enteric-coated tablet of rabeprazole as the source of the **PPI**. This tablet requires disintegration prior to use as a liquid formulation. Part 1 (the low concentration of Secondary Essential Buffer). . .
DETD

Formulation 26: Unflavored Rabeprazole Powder (single dose)

PPI:
Rabeprazole sodium powder USP 20 mg
Primary Essential Buffer(s):
Calcium lactate USP 700 mg
Calcium glycerophosphate 700 mg
Secondary. . .
DETD

Formulation 27: Unflavored Esomeprazole Powder (single dose)

PPI:
Esomeprazole magnesium powder USP 20 mg
Primary Essential Buffer(s):

Calcium lactate USP 800 mg
Calcium glycerophosphate 800 mg
Secondary. . .
DETD

Formulation 28: Omeprazole Two Part Tablet
Two part tablets contain an outer buffer phase and inner buffer/**PPI** core.
Enough for 6 tablets is weighed out.

Inner Core:
PPI:
Omeprazole powder USP 120 mg
(or esomeprazole magnesium or omeprazole sodium).
Primary Essential Buffer(s):
Sodium bicarbonate USP 1200 mg
Outer Phase:
Sodium bicarbonate USP 3960 mg

(Secondary. . .
DETD The outside layer surrounding the **PPI** tablet serves as a pH-buffering zone. Enough sodium bicarbonate for 6 tablets is weighed out with approximately 280 mg per. . .
DETD

Formulation 29: Lansoprazole Two Part Tablet
Enough for 6 tablets is weighed out.

Inner Core:
PPI:
Lansoprazole powder USP 180 mg
Primary Essential Buffer:
Sodium bicarbonate USP 1200 mg
Outer Phase:
Sodium bicarbonate USP 3960 mg
DETD

Formulation 30: Pantoprazole Two Part Tablet
Enough for 6 tablets is weighed out.

Inner Core:
PPI:
Pantoprazole powder USP 240 mg
(or pantoprazole sodium)
Primary Essential Buffer:
Sodium bicarbonate USP 1200 mg
Outer Phase:
Sodium bicarbonate. . .
DETD

Formulation 31: Omeprazole or esomeprazole two part tablet.
Enough for 6 tablets is weighed out.

Inner Core:
PPI:
Omeprazole powder USP (or esomeprazole or 120 mg
omeprazole sodium).
Primary Essential Buffer:
Sodium bicarbonate 1200 mg
Outer Phase:
Sodium. . .
DETD

Formulation 32: Lansoprazole Two part tablet
Enough for 6 tablets is weighed out.

Inner Core:
PPI:

Lansoprazole powder USP 180 mg
Primary Essential Buffer:
Sodium bicarbonate 1200 mg
Outer Phase:
Sodium bicarbonate 3960 mg
DETD

Formulation 33: Pantoprazole Two part tablet
Enough for 6 tablets is weighed out.

Inner Core:
PPI:
Pantoprazole sodium powder USP 240 mg
Primary Essential Buffer:
Sodium bicarbonate 1200 mg
Outer Phase:
Sodium bicarbonate 3960 mg
DETD

Formulation 34: Omeprazole 20 mg Two-Part Tablet

Inner Core:
PPI:
Omeprazole enteric coated granules (base, or 20 mg
sodium salt or esomeprazole sodium or magnesium)
Outer Phase:
Sodium bicarbonate powder. . .
DETD . . . the inner core as described in Formulation 28. Other variations of this tablet include a uniform enteric coating surrounding the **PPI** of the inner core instead of separate enteric coated granules.
DETD

Formulation 35: Lansoprazole 30 mg Two-Part Tablet

Inner Core:
PPI:
Lansoprazole enteric coated granules 30 mg
Outer Phase:
Sodium bicarbonate powder USP 1000 mg
DETD

Formulation 36: Rabeprazole 20 mg Two-Part Tablet

Inner Core:
PPI:
Rabeprazole enteric coated granules 20 mg
Outer Phase:
Sodium bicarbonate powder USP 1000 mg
DETD

Formulation 38: Combination **Antacid**
and Enteric Coated Dosage Form

Omeprazole enteric coated granules or 20 mg (or an equivalent dose of another **PPI**)
enteric coated tablet
Calcium carbonate 1000 mg
DETD . . . in either a compressed tablet or in a larger capsule. In another embodiment, a capsule containing enteric coated granules of **PPI** can be placed within a larger capsule containing the calcium carbonate.
DETD

Formulation 39: Combination Rapid
Release and Delayed Released **PPI** and
Antacid

Inner core: 10 or 20 mg (or an equivalent dose of another
Omeprazole enteric coated granules or **PPI**)
enteric coated tablet
Outer phase:
Omeprazole powder 10 or 20 mg (or equivalent dose of another
PPI)
Calcium Carbonate powder 1000 mg
DETD Formulation 40: Soft Chewable **PPI**-Buffer Dosage Form
DETD Omeprazole 10 or 20 mg (or an equivalent dose of another **PPI**) is combined with the ingredients of a soft chewable **antacid** tablet (e.g., Viactiv®), which comprises calcium carbonate 500 or 1000 mg, corn syrup, sugar, chocolate non fat milk, cocoa butter,. . .
CLM What is claimed is:
. . . A solid oral pharmaceutical dosage form that is not enteric-coated, comprising: active ingredients consisting essentially of: (a) at least one **proton pump inhibitor** (PPI) selected from the group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole, and an enantiomer, isomer, free base,. . . one optional Secondary Essential Buffer in a total amount of approximately 0.1 mEq to approximately 2.5 mEq per mg of **proton pump inhibitor**; and a pharmaceutically-acceptable excipient; wherein the dosage form is selected from the group consisting of a suspension tablet, chewable tablet,. . .
2. The dosage form of claim 1, wherein the **proton pump inhibitor** is in an amount from approximately 10 mg to approximately 100 mg.

3. The dosage form of claim 1, wherein the **proton pump inhibitor** is omeprazole.

4. The dosage form of claim 1, wherein the **proton pump inhibitor** is lansoprazole.

5. The dosage form of claim 1, wherein the **proton pump inhibitor** is pantoprazole.

6. The dosage form of claim 1, wherein the **proton pump inhibitor** is rabeprazole.

7. The dosage form of claim 1, wherein the **proton pump inhibitor** is esomeprazole.

8. The dosage form of claim 1, wherein the **proton pump inhibitor** is pariprazole.

9. The dosage form of claim 1, wherein the **proton pump inhibitor** is leminoprazole.

. . . of at least one Primary Essential Buffer; and the inner core comprising active ingredients consisting essentially of at least one **proton pump inhibitor** selected from the group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole, or an enantiomer, isomer, free base,. . . from the group consisting of a Primary Essential Buffer and a Secondary Essential Buffer; wherein the total amount of the **proton pump inhibitor** is approximately 5 mg to approximately 300 mg; and the total amount of the buffering agent is approximately 0.1 mEq to approximately 2.5 mEq per mg of **proton pump inhibitor**.

. . . effective to elevate pH of gastric fluid of the subject upon oral administration to at least 3.7 from time the **proton pump inhibitor** comes in contact with the gastric fluid throughout dwell time in the stomach.

29. A non-enteric coated solid oral pharmaceutical dosage form, comprising: (a) active ingredients consisting essentially of: (i) a **proton pump inhibitor** (PPI) selected from the group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole, and an enantiomer, isomer, free base,. . . one optional Secondary Essential Buffer in a total amount of approximately 0.1 mEq to approximately 2.5 mEq per mg of **proton pump inhibitor**; and (b) a pharmaceutically-acceptable excipient; wherein

the dosage form is created by a method comprising: i) blending the **proton pump inhibitor**, the Primary Essential Buffer, the optional Secondary Essential Buffer, and the pharmaceutically-acceptable excipient; and ii) formulating the **proton pump inhibitor**, the Primary Essential Buffer, the optional Secondary Essential Buffer, and the pharmaceutically-acceptable excipient into a powder, tablet, suspension tablet, chewable. . .

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	65.05	111.26

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